Amyloid Cardiomyopathy: New Perspectives on an Old Disease

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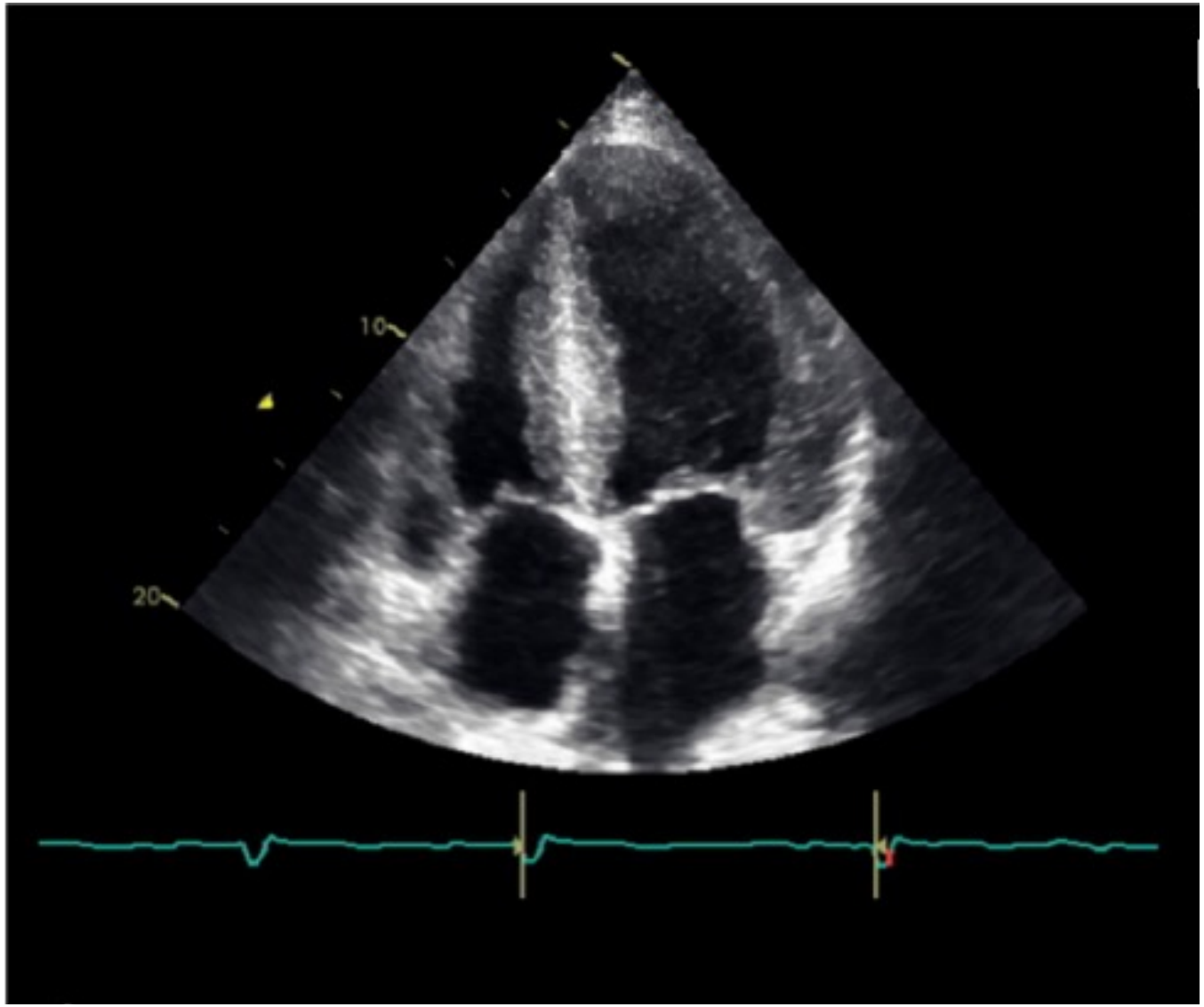
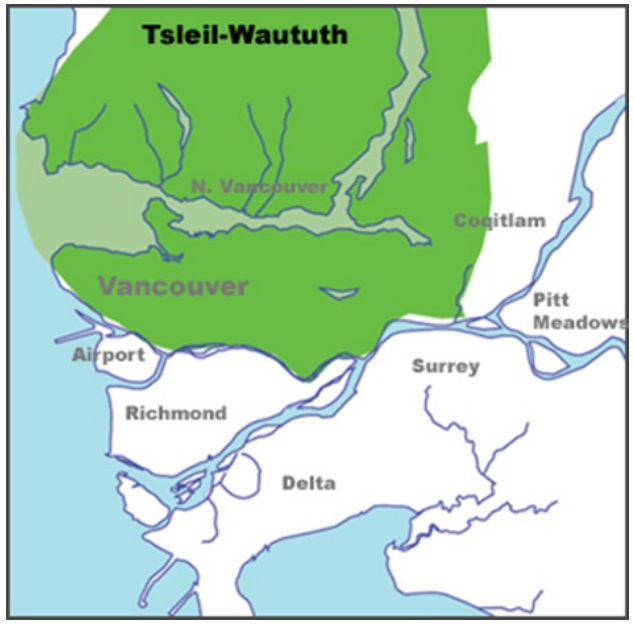


We would like to acknowledge that we are gathered today on the traditional territories of the Musqueam, Squamish and Tsleil-Waututh peoples.

Source: www.johomaps.net/na/canada/bc/vancouver/firstnations/firstnations.html



Disclosures

- **Consultancy/speaking fees**: Janssen, Novartis, Boehringer-Ingelheim, Takeda, Pfizer, Akcea, Alnylam, Amgen, Ferring

- **Grant funding**: Pfizer, Takeda, Boehringer-Ingelheim, Servier, Akcea

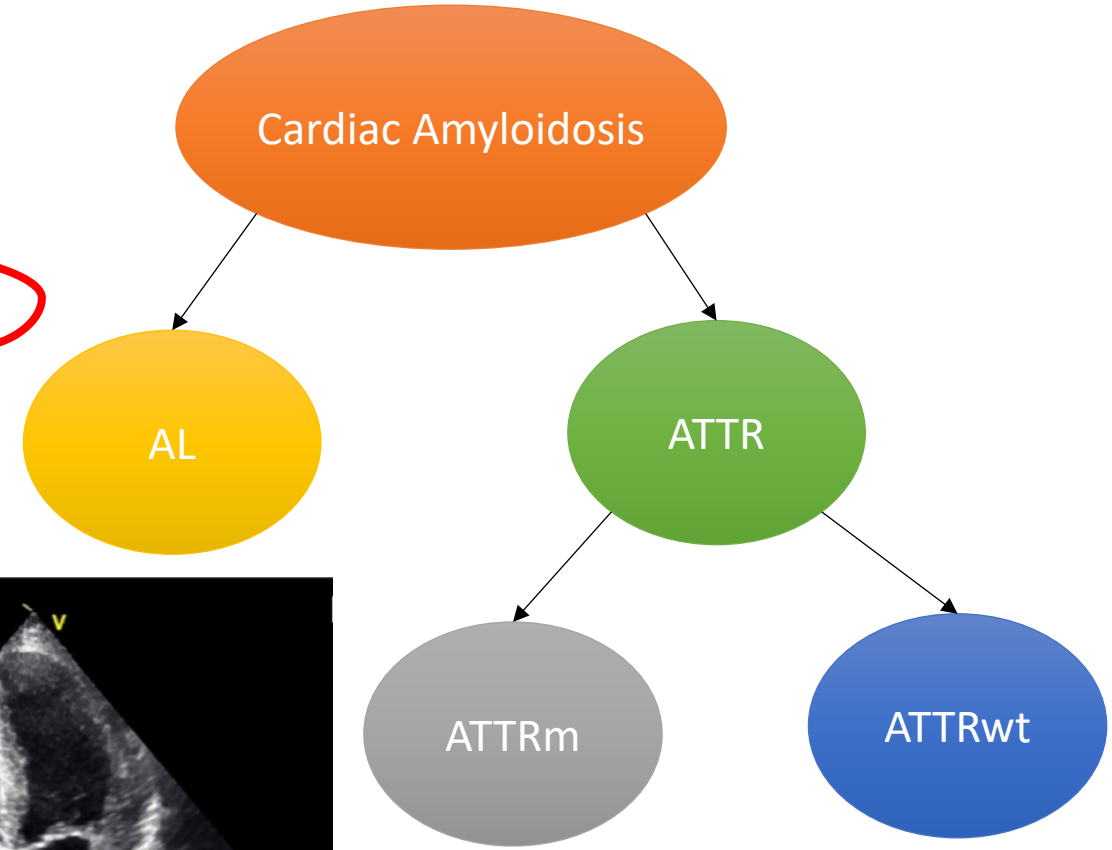
Objectives

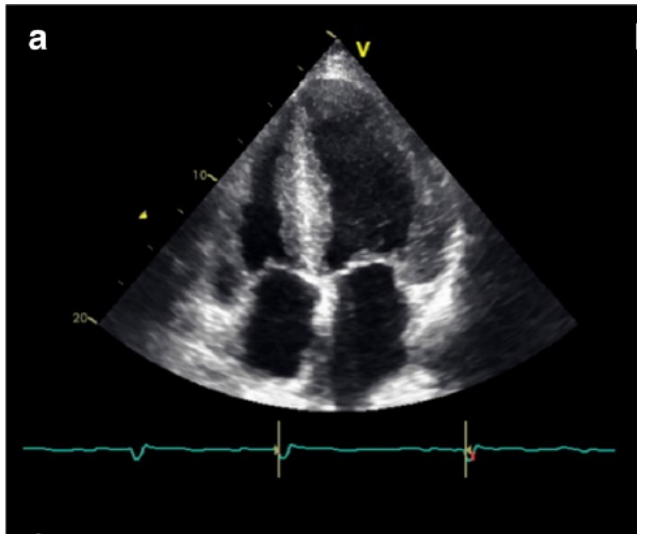
- Outline “red flag” signs and symptoms and screening tools to diagnose Cardiac Amyloidosis
- Outline and approach to the diagnosis of AL vs ATTR Amyloidosis
- Discuss efficacy and safety data of new therapeutic options in ATTR-CM
- Identify the clinical practice considerations for managing patients with cardiac amyloidosis

Cardiac Amyloidosis

- **Majority of cardiac amyloidosis is caused by**
- Light chains (AL): 65-80% of all *diagnosed* cases
- Transthyretin (ATTR): 18-35% of all *diagnosed* cases

- **2 distinct types of ATTR**
- Hereditary or mutated (ATTRm)
- Wild-type (ATTRwt), also known as:
  - Senile systemic amyloidosis
  - Age-related amyloidosis
  - Senile cardiac amyloidosis

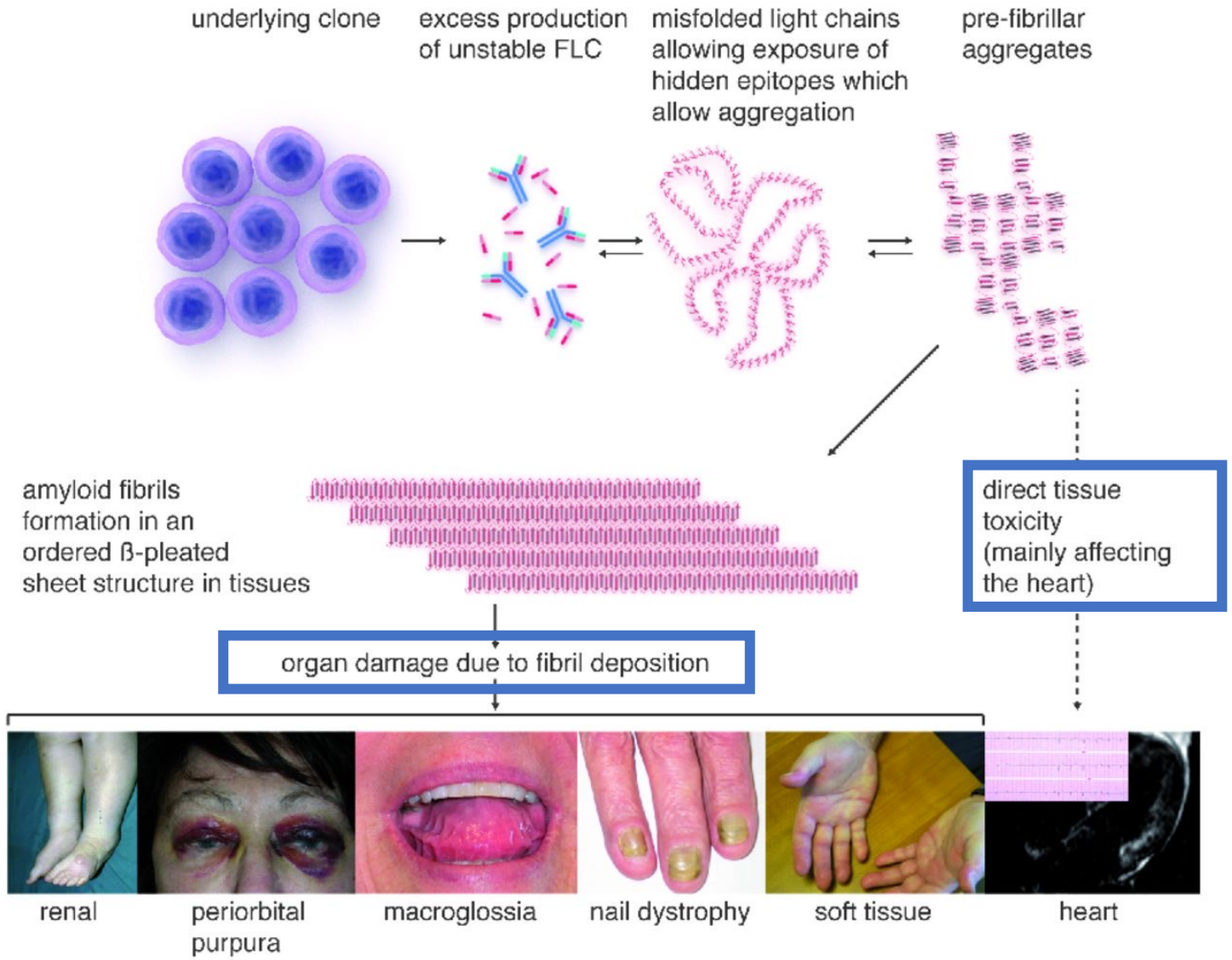




AL, light-chain amyloidosis; ATTR, transthyretin amyloidosis; m, mutated; wt , wild-type.

Maleszewski JJ. Cardiovascular Pathology 2015;24(6):343-350; Rapezzi C et al. Circulation 2009;120:1203-1212; Maurer MS et al. J Am Coll Cardiol 2016;68(2):161-172.

Pathobiology of AL Amyloid



Haematologica 2014;99:209-221

AL Amyloid: Epidemiology

AL is still a rare disease - annual incidence:

- ~10/1,000,000

Prevalence:

- ~50/1,000,000 person-years

Mean age at diagnosis:

- 63

Male-female ratio:

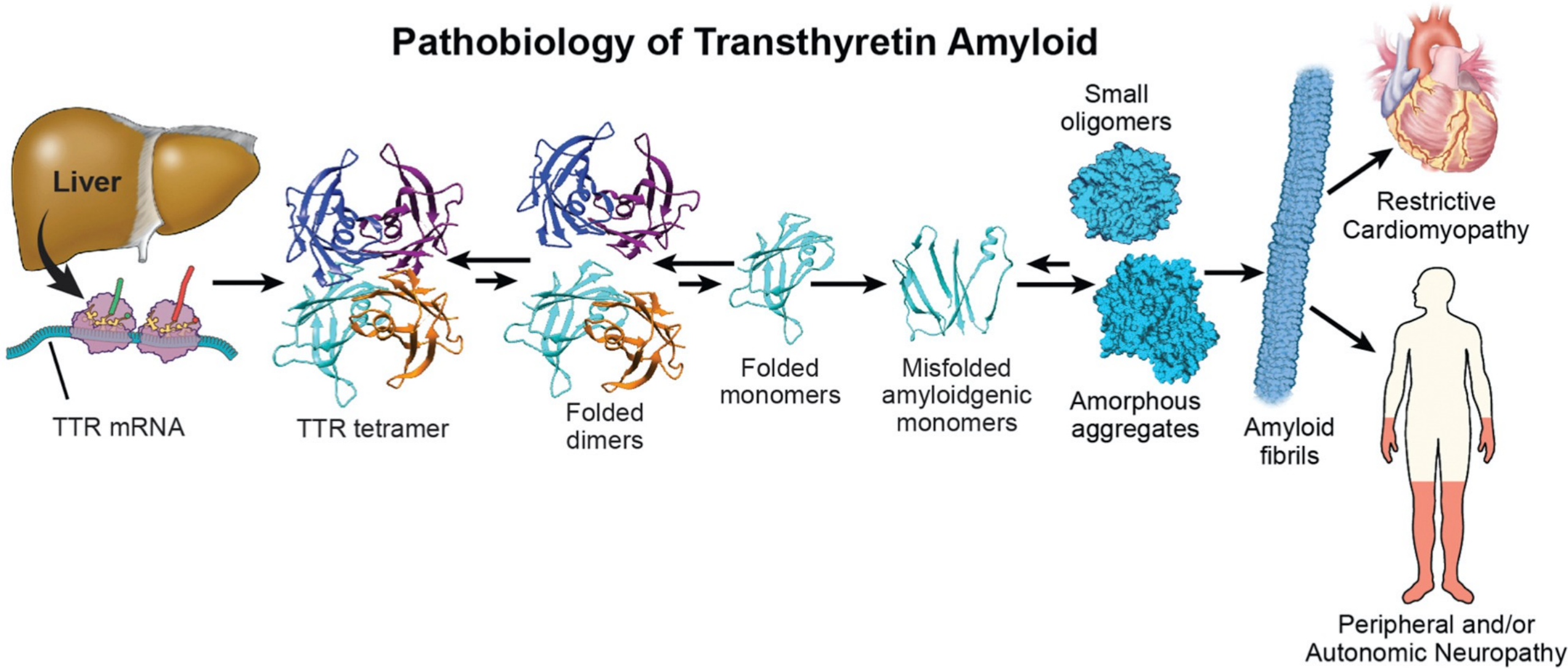
- 55/45

Risk factors:

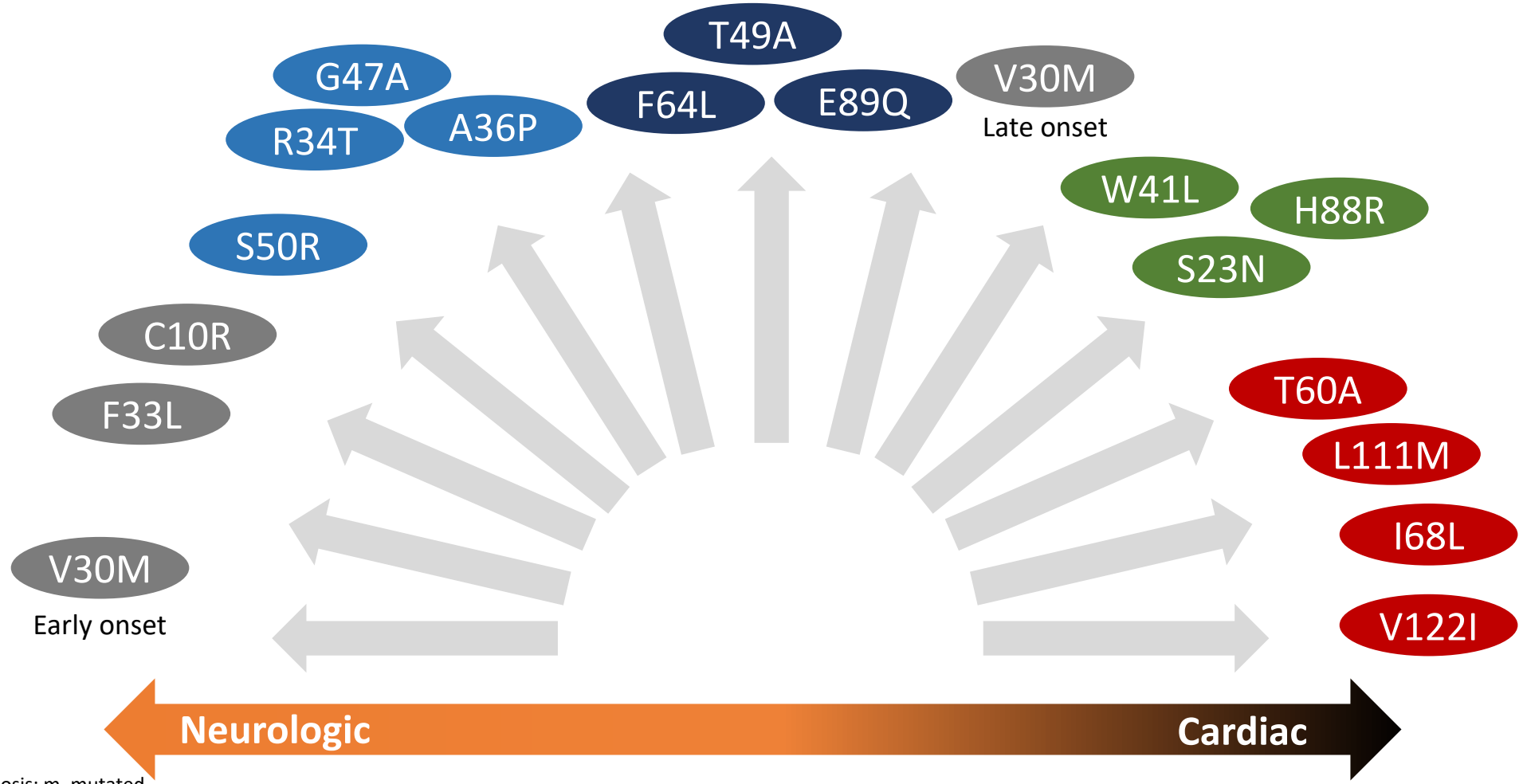
- MGUS
- Genetic predisposition?

Haematologica 2014;99:209-221

Pathobiology of Transthyretin Amyloid



Spectrum of Genotype-Phenotype Correlation in hATTR



ATTR, transthyretin amyloidosis; m, mutated.
Adapted from Rapezzi C et al. European Heart Journal 2013;34:520-528.

Characteristics of Wild-type and Common Variant TTR Cardiac Amyloidosis

Mutation	Origin	Prevalence	Male:Female Ratio	Onset	Organs
ATTRwt	World wide	25% >85 yrs	25-50:1	>60 yrs	Heart, ST
V122I	US Caribbean Africa	4% African American	1:1 gene (+) 3:1 disease	>65 yrs	Heart, PNS, ST
V30M	Portugal Sweden Japan	1:1000	2:1	>50 yrs	PNS/ANS, heart
T60A	UK Ireland	1% Northwest Ireland	2:1	>45 yrs	Heart, PNS/ANS

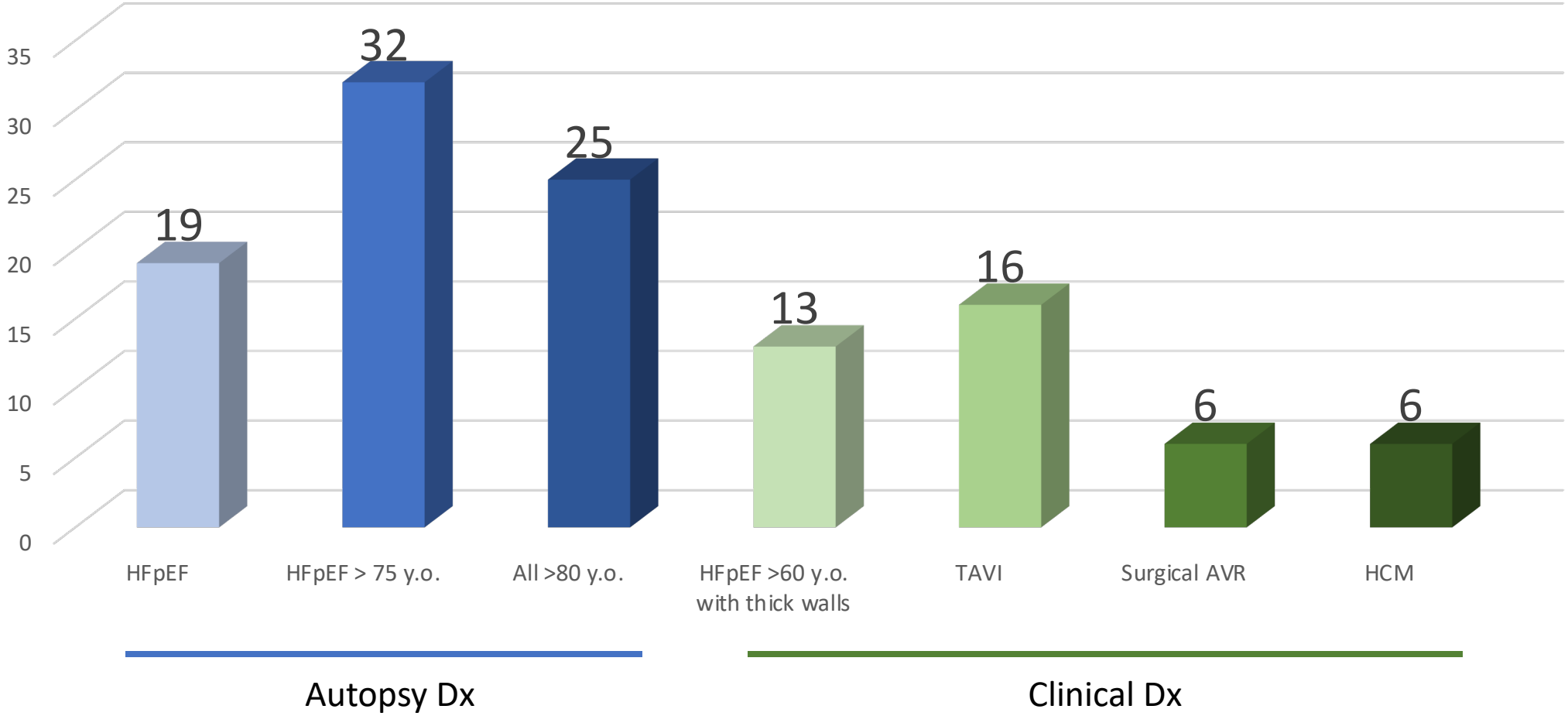
ANS, autonomic nervous system; ATTRwt, wild-type transthyretin amyloidosis; PNS, peripheral nervous system; ST, soft tissue; TTR, transthyretin; yrs, years; UK, United Kingdom; US, United States.
Adapted from Ruberg FL, Berk JL. Circulation 2012;126(10):1286-1300.

Epidemiology of wtATTR

- Accurate population data are limited
- Wild-type disease is far more common than mutant
- Clinical features mimic other cardiac pathologies that frequently co-exist in advanced age, such as hypertensive heart failure and aortic stenosis

ATTR, transthyretin amyloidosis; ATTR-CA, transthyretin cardiac amyloidosis; ATTRwt, wild-type form of transthyretin amyloidosis; CA, cardiac amyloidosis; HFpEF, heart failure with preserved ejection fraction; TAVR, transcatheter aortic valve replacement.

Connors LH et al. Circulation 2016;133(3):282-290; González-López E et al. Eur Heart J 2015;36(38) 2585-2594; Castaño A et al. Eur Heart J 2017;38(38):2879-2887.



Prevalence estimates of ATTR-CM

Cardiac Amyloidosis Is Characterized by Clinical Heterogeneity

- Nonspecific symptoms and manifestations overlap with more common disorders

- Misdiagnosis is common
  - A recent subanalysis of an Amyloidosis Research Consortium online survey revealed that:
    - Only 35% of ATTRwt and 17% of ATTRm were diagnosed in <12 months from start of symptoms
    - 39% of ATTRwt and 57% of ATTRm received a misdiagnosis
    - 17% of all respondents visited 5 different physicians before receiving the correct diagnosis

ATTRm, mutated transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; TTR, transthyretin.
Lousada I et al. Orphanet Journal of Rare Diseases 2017;12(Suppl 1):P7.

Comparison of Subtypes of Amyloid Cardiomyopathy

Amyloid Type	Systemic Amyloidosis	Transthyretin (TTR) Amyloidosis	
Subtype	**AL**	**ATTRm**	**ATTRwt**
Protein deposited	Light chain	Mutated TTR protein	wtTTR monomers
Disease etiology	Plasma cell dyscrasia with ↑ light chains	Familial mutation of TTR	Age-related TTR deposition - common in elderly aged >75 years
Specific features	Kidney, heart, nerves, GI tract, and liver affected	V122I common in African Americans	Carpal tunnel Male dominance
Median survival	1-3 years	2 years	4-6 years
Prognostic factors	Cardiac function, BNP, troponin, FLC	Duration, ↓LVEF	BNP, uric acid, ↓LVEF, ↑ wall thickness

AA, amyloid A amyloidosis; AL, light-chain amyloidosis; ATTRm, mutated transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; BNP, brain natriuretic peptide; HR, heart rate; LVEF, left ventricular ejection fraction, TTR, transthyretin.

Adapted from Liu PP, Smyth D. Circulation. 2016;133:245-247.

Amyloid CM: Suspicion to Diagnosis

Red flags and preliminary testing

Clinical presentation

Biomarkers

ECG

Echo

CMR

Diagnostic testing

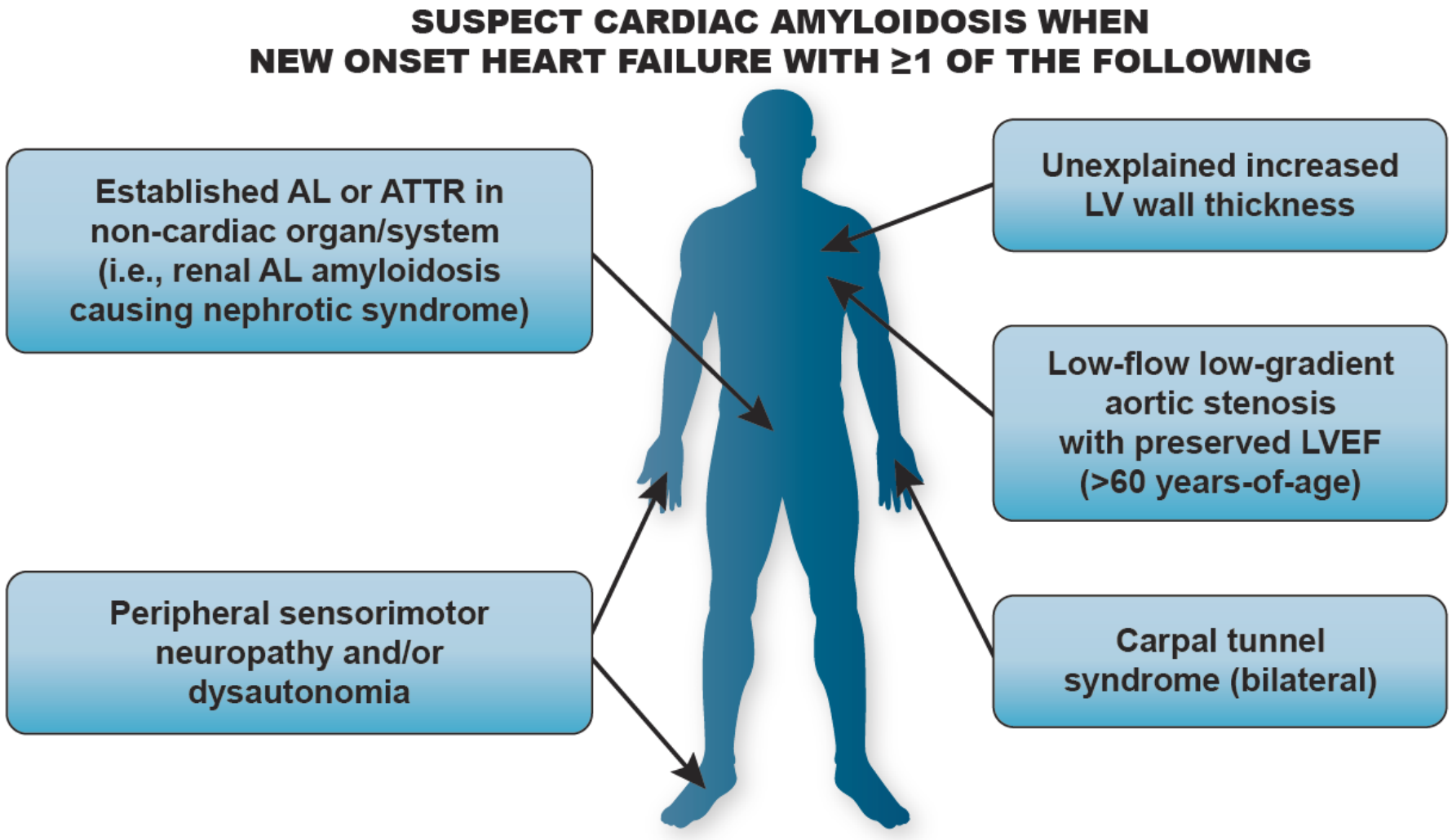
Noninvasive: PYP and SPIE/UPIE/FLC

Invasive: Biopsy and mass spec

Cardiac Manifestations

- Heart failure - frequently biventricular, typically preserved LVEF
- Atrial fibrillation
- Conduction system disease
- Ventricular arrhythmia - may be asymptomatic
- Aortic stenosis - low-flow low-gradient for wtATTR, typically with preserved LVEF

Index of Suspicion – Key Features



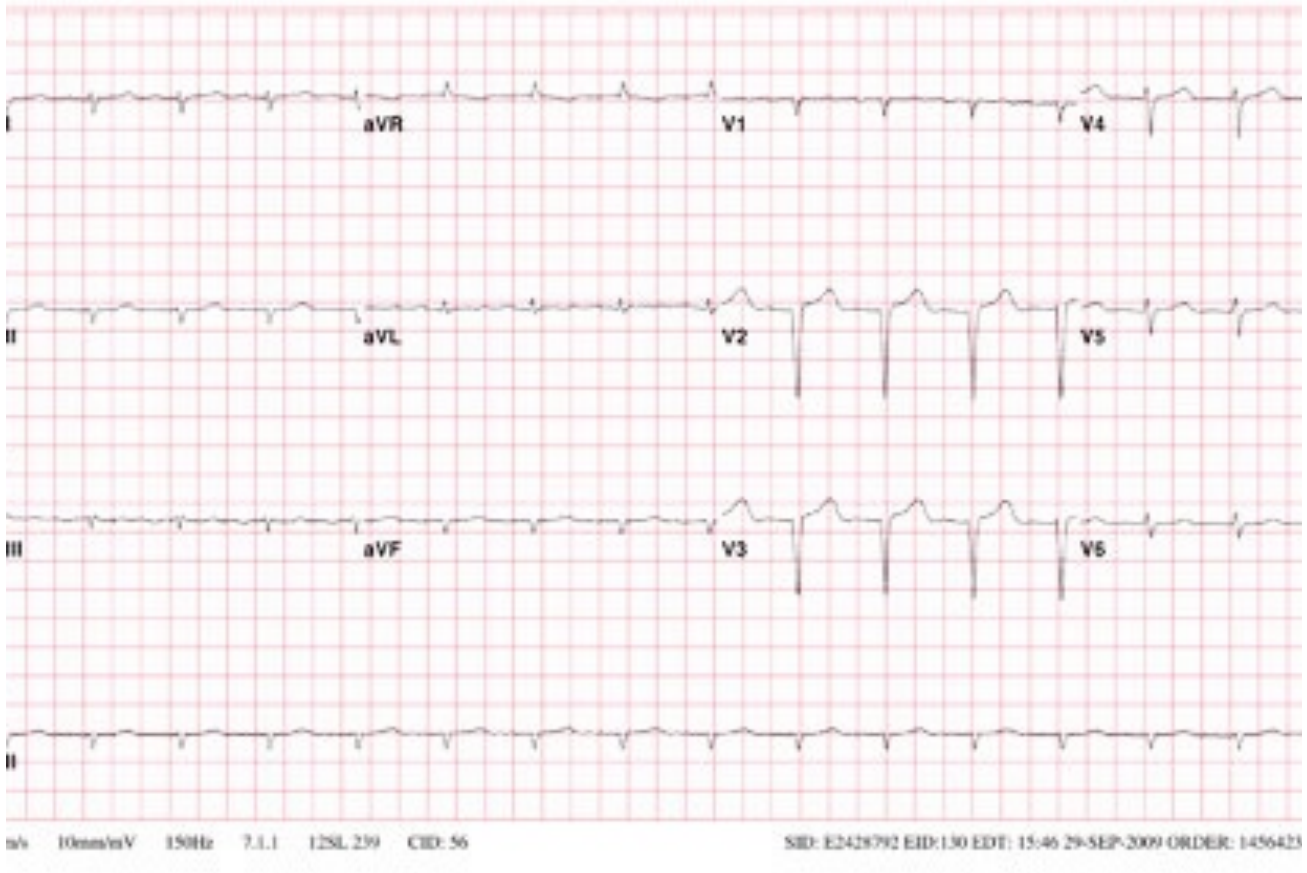
Clinical Scenarios that Warrant Screening for Amyloid CM: "Red flag" Signs and symptoms

- Reduction in LV longitudinal strain with apical sparing
- Discrepancy between LV thickness and QRS voltage
- AV block, in the presence of increased LV wall thickness
- Echo hypertrophic phenotype with associated infiltrative features, including increased thickness of the AV valves, interatrial septum and RV wall
- Marked extracellular volume expansion, or diffuse late gadolinium enhancement on cardiac MR
- Symptoms of polyneuropathy and / or dysautonomia
- History of bilateral carpal tunnel syndrome
- Mild increase in troponin levels on repeated occasions

Witteles RM, et al. *JACC Heart Fail* 2019; 7(8):709–16.

ECG in Cardiac Amyloidosis

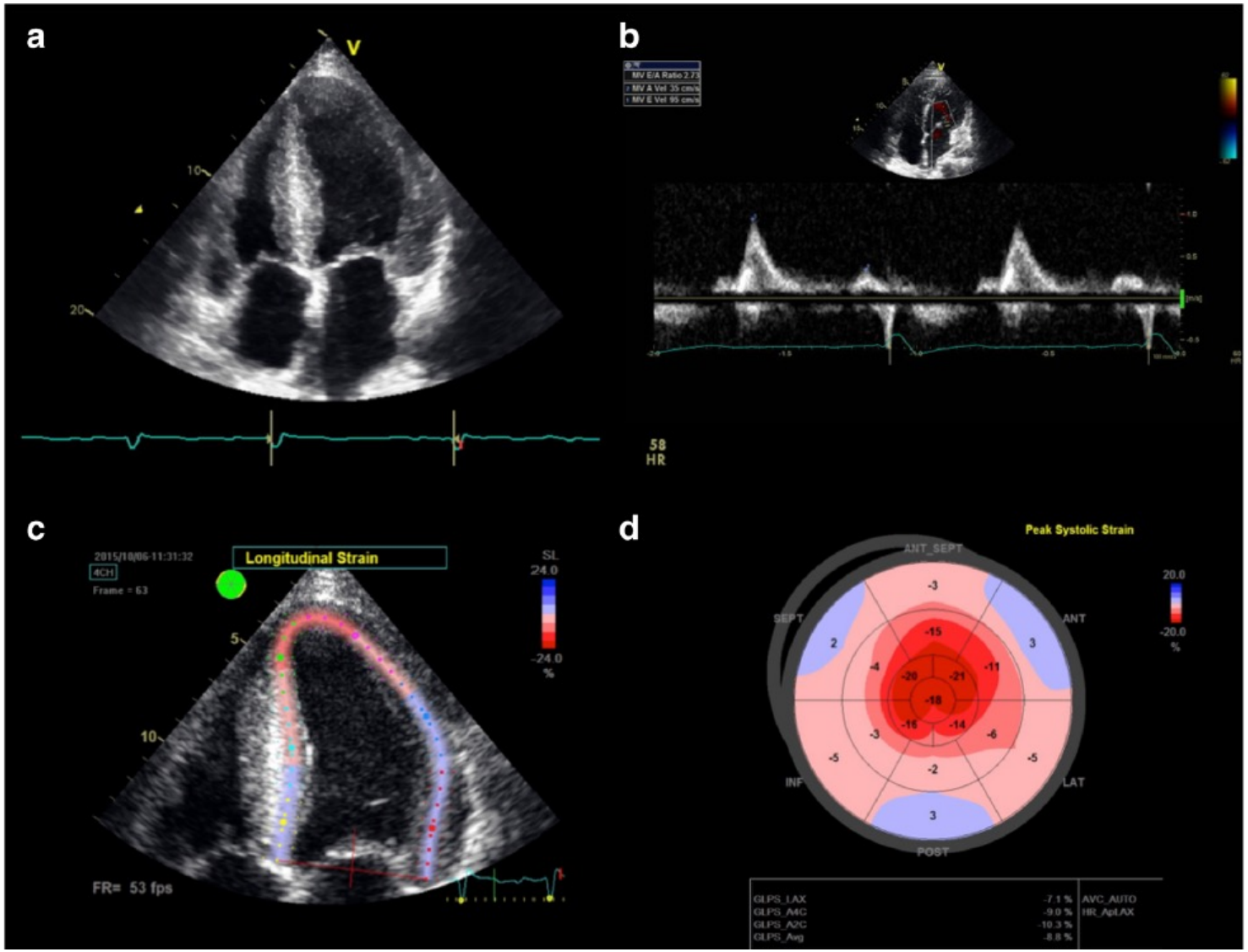
- Low ECG voltage in 46-56%
  - May have LVH on ECG
- Pseudoinfarct pattern in 47-60%
  - Anterior 36%, inferior 12%, lateral 14%
- Low voltage + pseudoinfarct in 25%
  - Sn 72% and Sp 91%
- AF/flutter in 25% with increased LV wall thickness, 7% without
- Ventricular ectopy
- Conduction system disease
- ***Findings neither sensitive nor specific***



1. Am J Cardiol 2005;95:535-7
2. JACC 2004;43:410-5
3. Am Heart J 1997;134:994-1001

Echocardiogram in Cardiac Amyloidosis

Biventricular increased wall thickness, biatrial enlargement, thick IAS



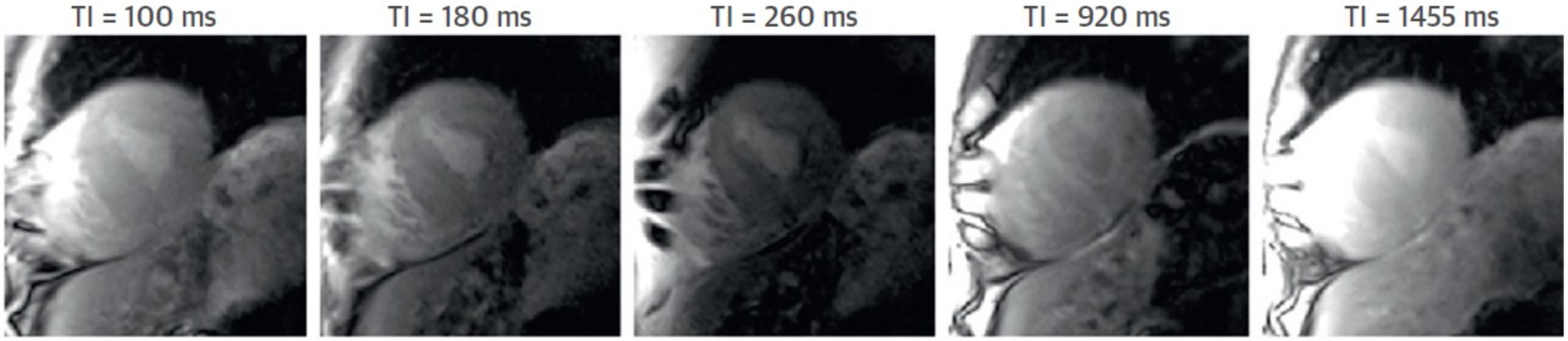
Restrictive diastolic filling pattern

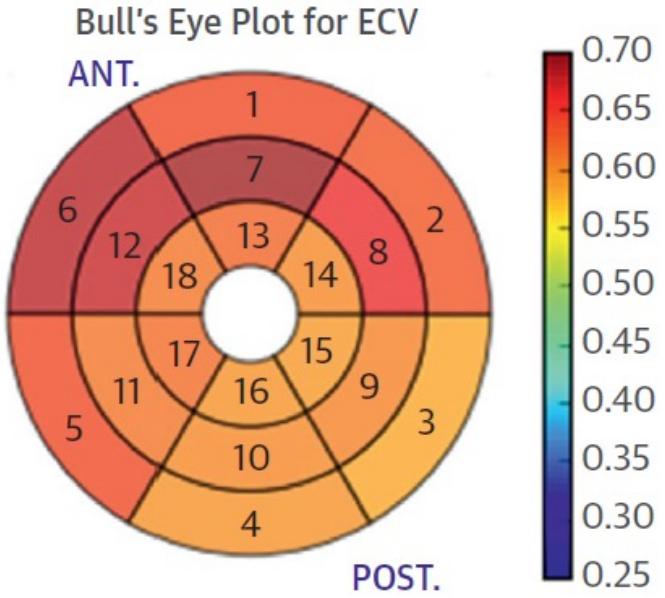
Reduced global longitudinal systolic strain

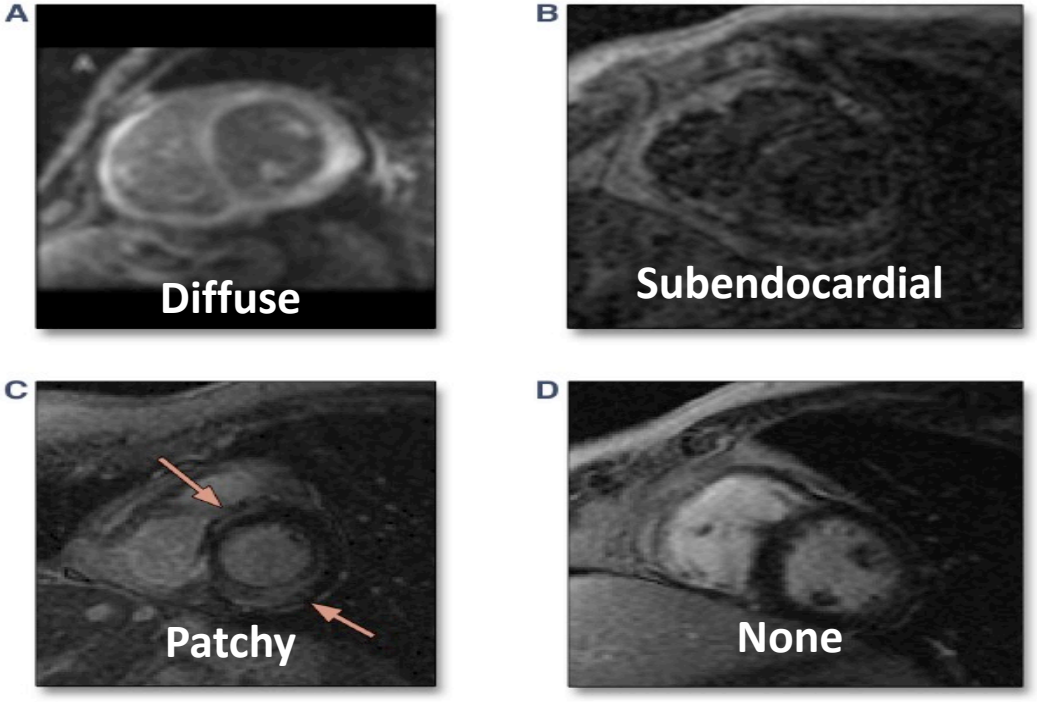
Preserved apical longitudinal systolic strain

White JA, Fine NM. Curr Cardiol Rep 2016;18 (8):77

cMRI in Cardiac Amyloidosis







ANT, anterior; ECV, extracellular volume; LGE, late gadolinium enhancement; MI, myocardial infarction; MRI, magnetic resonance ima

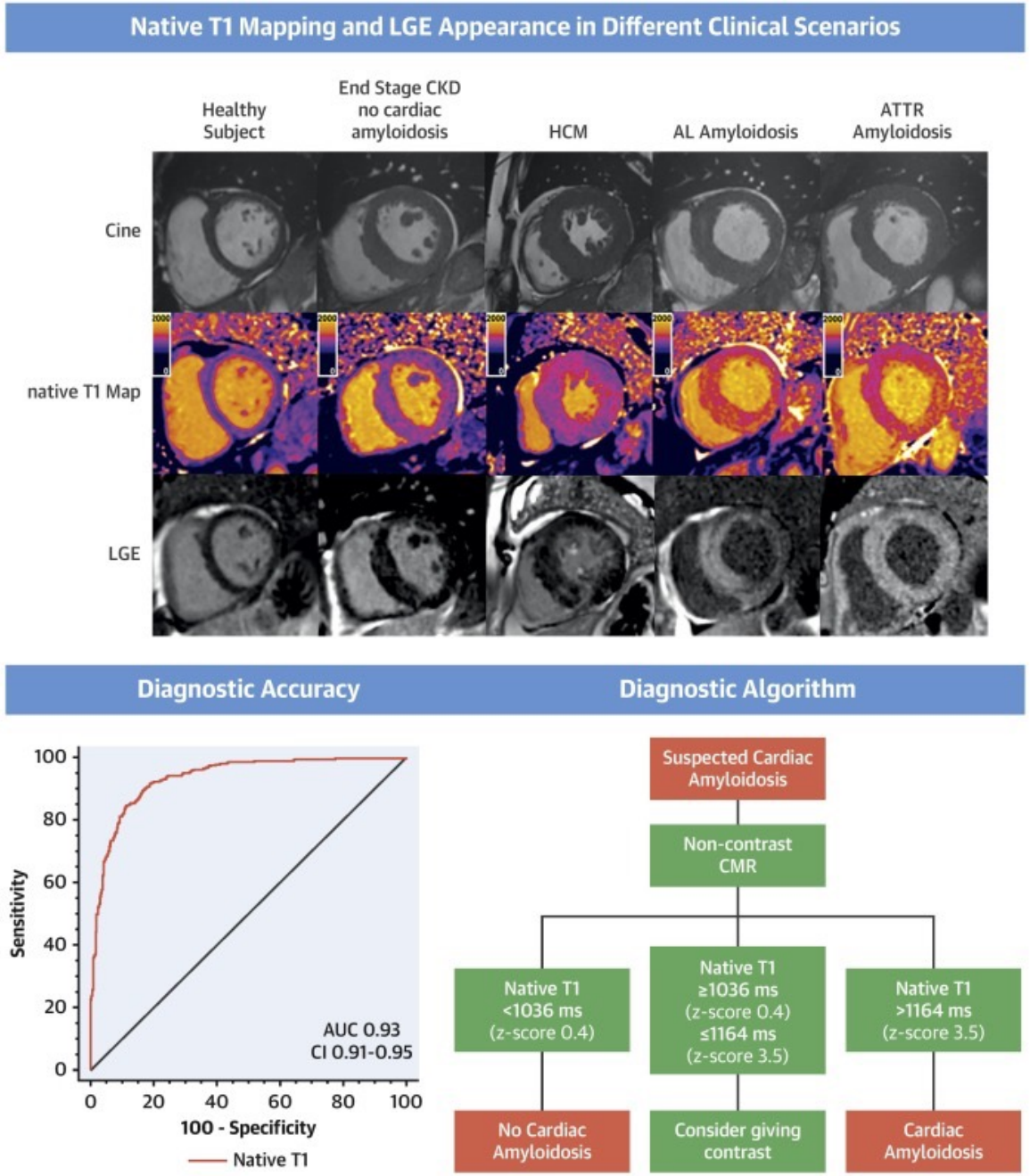
Falk RH et al. J Am Coll Cardiol 2016;68(12):1323-1341, Boynton et al. JACC CV Img 2016;9:680.

Typical CMR Imaging Features of Cardiac Amyloidosis

Parameters	Comments
Characteristic morphological features of cardiac amyloidosis/restrictive cardiomyopathy	• Better spatial resolution than echocardiography • No limitation of difficult echo windows
Left ventricular LGE	• Diffuse and subendocardial LGE of the LV myocardium is more common than patchy focal delayed enhancement • May be an early feature of cardiac involvement compared to increased wall thickness
Atrial LGE and dysfunction	• A common feature of cardiac amyloidosis
T1 mapping	• Subendocardial T1 relaxation time may be shortened in cardiac amyloidosis • This is an early feature of cardiac amyloid involvement
Extracellular volume estimation based on T1 mapping and hematocrit measures	• Extracellular volume expansion may permit an early diagnosis of cardiac amyloid even before overt left ventricular LGE

CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; LV, left ventricle.
Falk RH et al. Circ Cardiovasc Imaging 2014;7(3):552-562.

Native T1 in Cardiac Amyloidosis



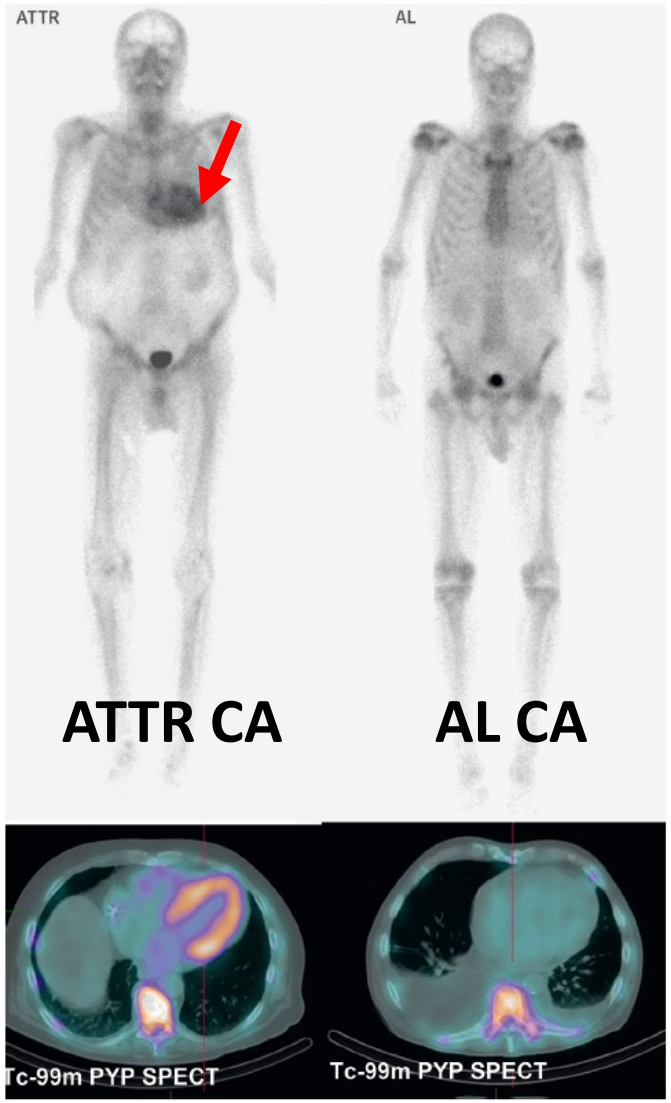
Baggiano, A. et al. J Am Coll Cardiol Img. 2020;13(1P1):69-80.

Tc99m-PYP SPECT in ATTR Cardiac Amyloidosis

Intense diffuse myocardial uptake in a patient with ATTR cardiac amyloidosis, grade 2-3 compared with bone

No/minimal myocardial uptake in a patient with AL cardiac amyloidosis, or other causes of LVH

Heart : Contralateral lung ratio >1.5 or grade 2-3 highly sensitive and specific for ATTR cardiac amyloidosis



Planar whole body scan

With SPECT

CAVEATS

Reported sensitivities and specificities are from experienced labs

Important to confirm myocardial uptake with SPECT imaging to differentiate from blood pool

Reported specificity only applies to patients with negative AL workup:

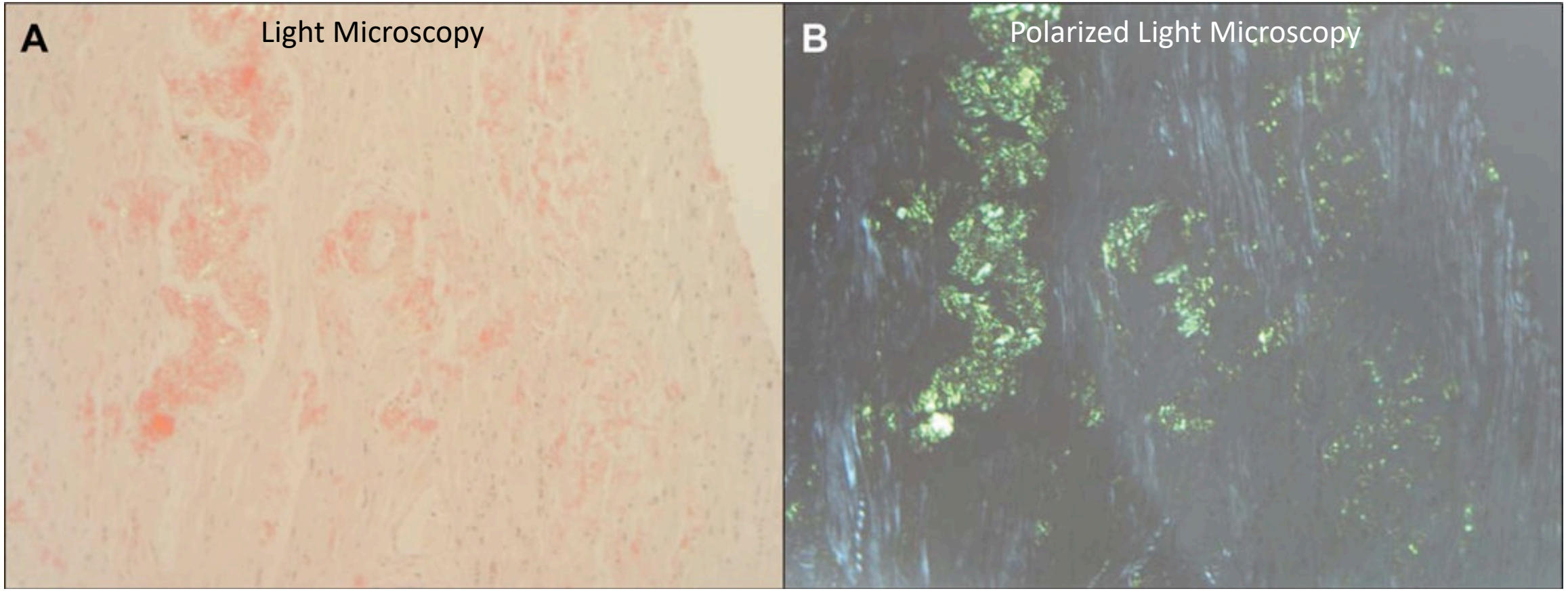
- SPEP/UPEP with IFE
- Serum FLC ratio

Must rule out AL in order to interpret test properly

ATTR, transthyretin amyloidosis; SPECT, single photon emission computed tomographyTc99m-PYP, ^{99m}technetium pyrophosphate.

J Am Coll Cardiol, 68(12), Falk RH et al., 1323-1341, (2016)

Endomyocardial Biopsy in Cardiac Amyloidosis



A) Light microscopy, and B) polarized light microscopy, 400X magnification.
Ruberg FL, Berk JL, Circulation 2012;126(10):1286-1300.

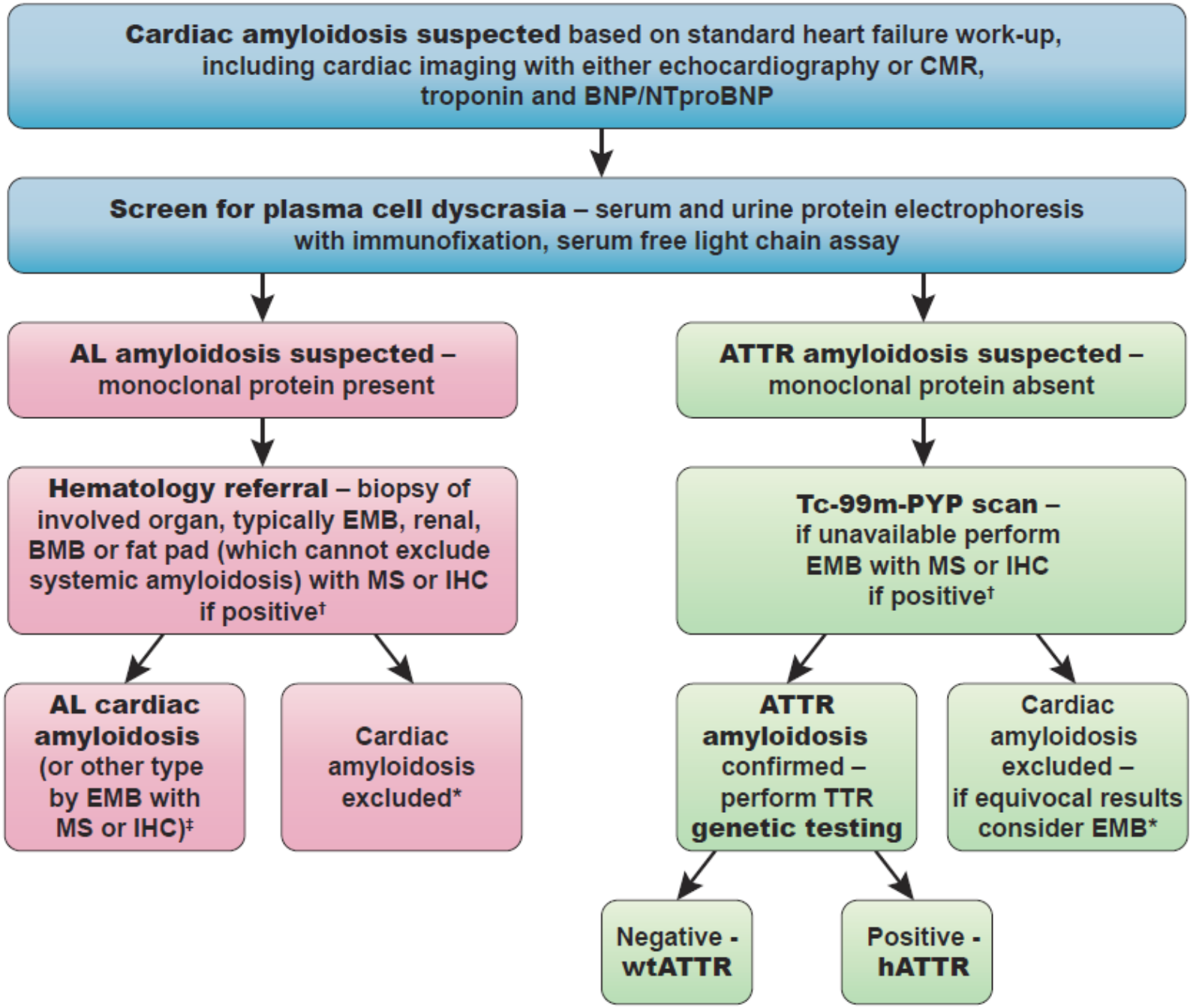
Dave: 76M with HFpEF, NYHA 2, 14 mm walls, no HTN or LVH on ECG, BNP 790

SPEP/UPEP/IFE N
K/L 3.2

EMBx: amyloid
Mass spec: ATTR

Genetic testing:
No mutation *TTR*

Dave has wtATTR



Rose: 76F with AF, 12 mm walls, GLS (-12)%, ap. sparing, bilat CTS

SPEP/UPEP/IFE N
K/L N

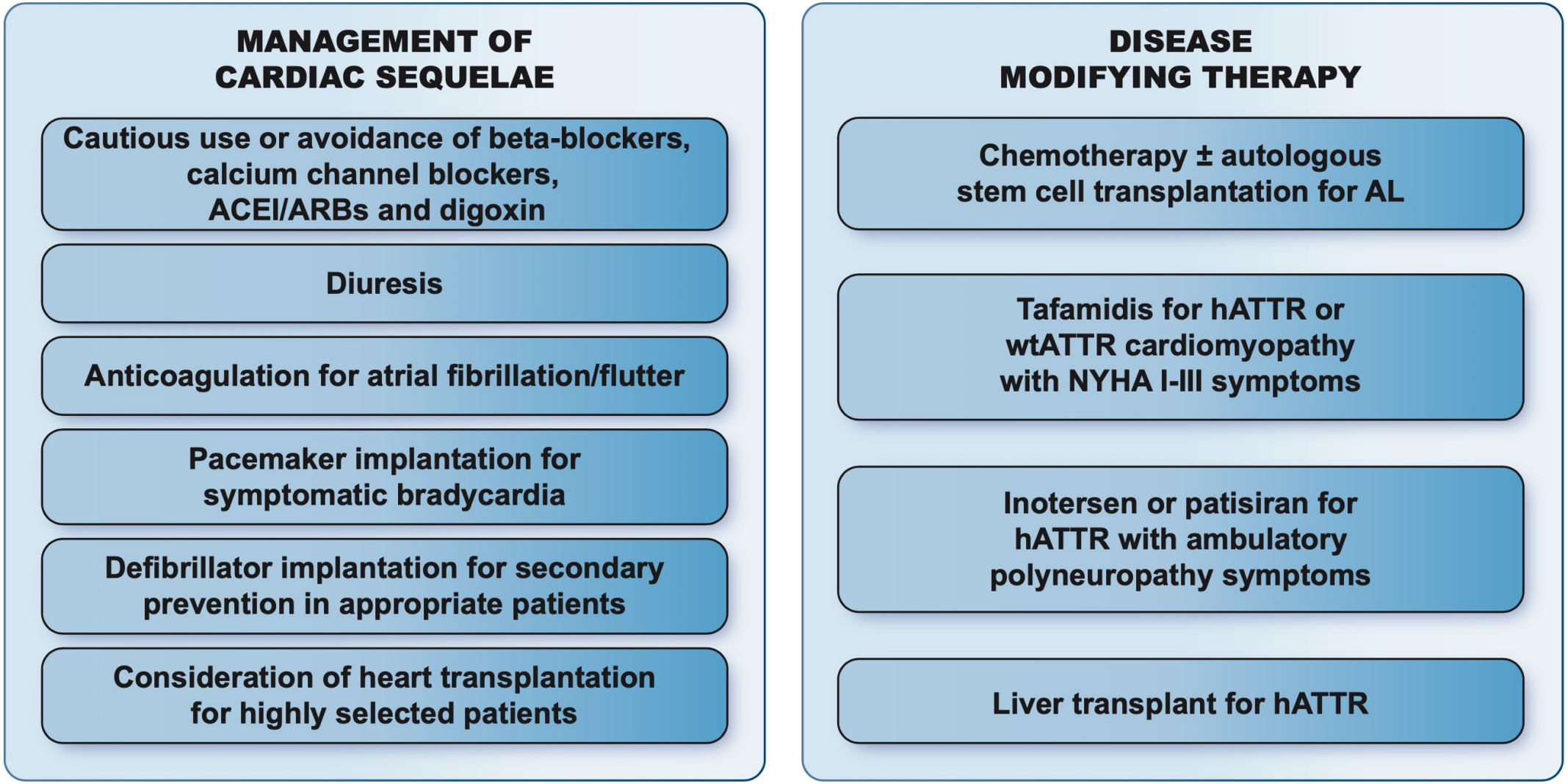
PYP Grade 2
H:CL 1.7

Genetic testing:
No mutation *TTR*

Rose has wtATTR

Management of Cardiac Amyloidosis

Overview of management



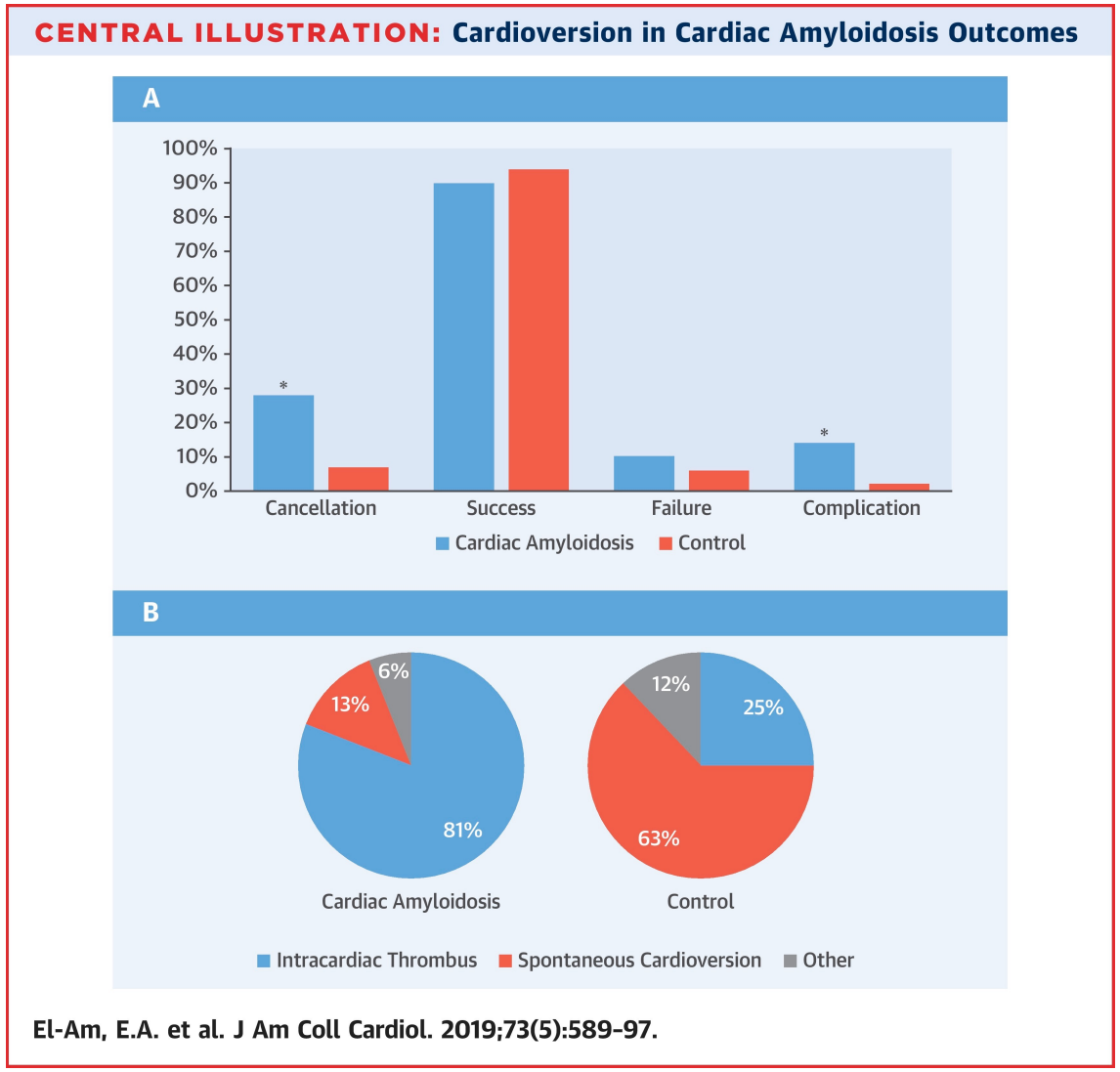
Supportive therapy for HF and AF in cardiac amyloidosis

Practical tip

- ***Beta-blockers, ACE inhibitors, and angiotensin receptor blockers (ARBs) are frequently poorly tolerated*** by patients with cardiac amyloidosis, and if indicated should be used with considerable caution. Furthermore, limited data and reports suggest an increased risk of ***local toxicity with digoxin and CCBs*** and these medications should be similarly used with caution or avoided altogether if possible.

Anticoagulation in AF and cardiac amyloidosis

- Of 13 cardiac amyloidosis patients with DCCV cancelled due to thrombus on TEE:
  - 2 had AF <48 hrs
  - 4 had INR >2 for >3 weeks



Anticoagulation in cardiac amyloidosis

Recommendation

- In the absence of contraindications, we recommend therapeutic anticoagulation in patients with cardiac amyloidosis and AF, ***regardless of calculated risk of stroke or systemic embolism***. (Strong Recommendation, Low-Quality Evidence).

Values and preferences

- Cardiac amyloidosis appears to be associated with a particularly high rate of left atrial thrombus, stroke, and systemic embolism. This risk is not captured with risk scores such as $CHADS_2$65 or $CHADS_2$-VaSC.

Anticoagulation in cardiac amyloidosis

Practical tip

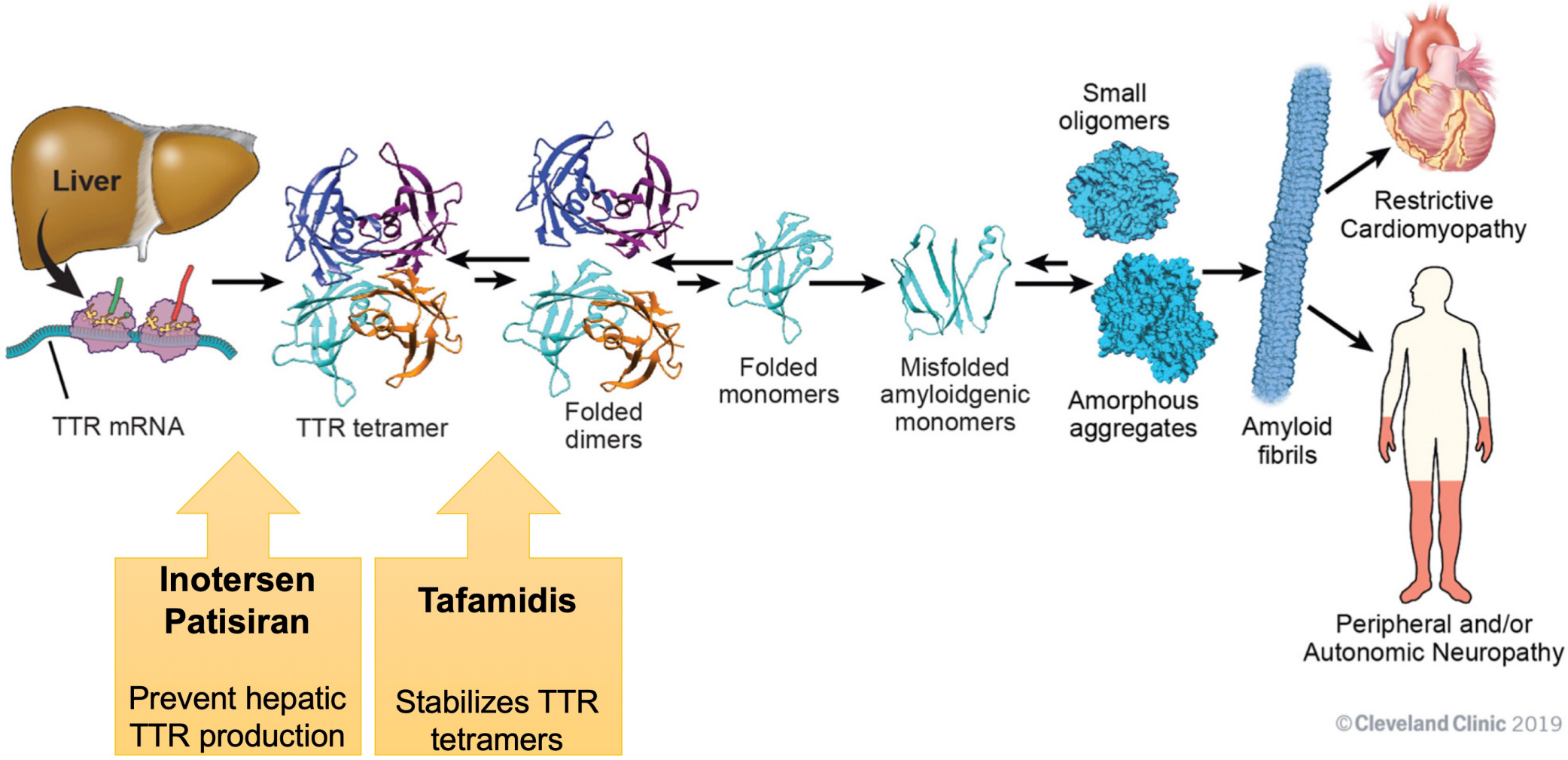
- While there are no data to inform the choice between warfarin and direct oral anticoagulants (DOACs), ***DOACs may be preferable*** due to the ease of administration and lower risk of intracranial hemorrhage.

Practical tip

- In patients with cardiac amyloidosis, high rates of left atrial thrombus have been reported on imaging and at autopsy, even in patients with adequate durations of therapeutic anticoagulation or with brief durations of AF. Thrombus has also been reported in patients in sinus rhythm. ***Transesophageal echocardiography should be considered prior to cardioversion*** in stable patients, regardless of duration of arrhythmia or anticoagulation.

Disease modifying therapy in ATTR

Therapeutic Targets of the Amyloidogenic TTR Cascade



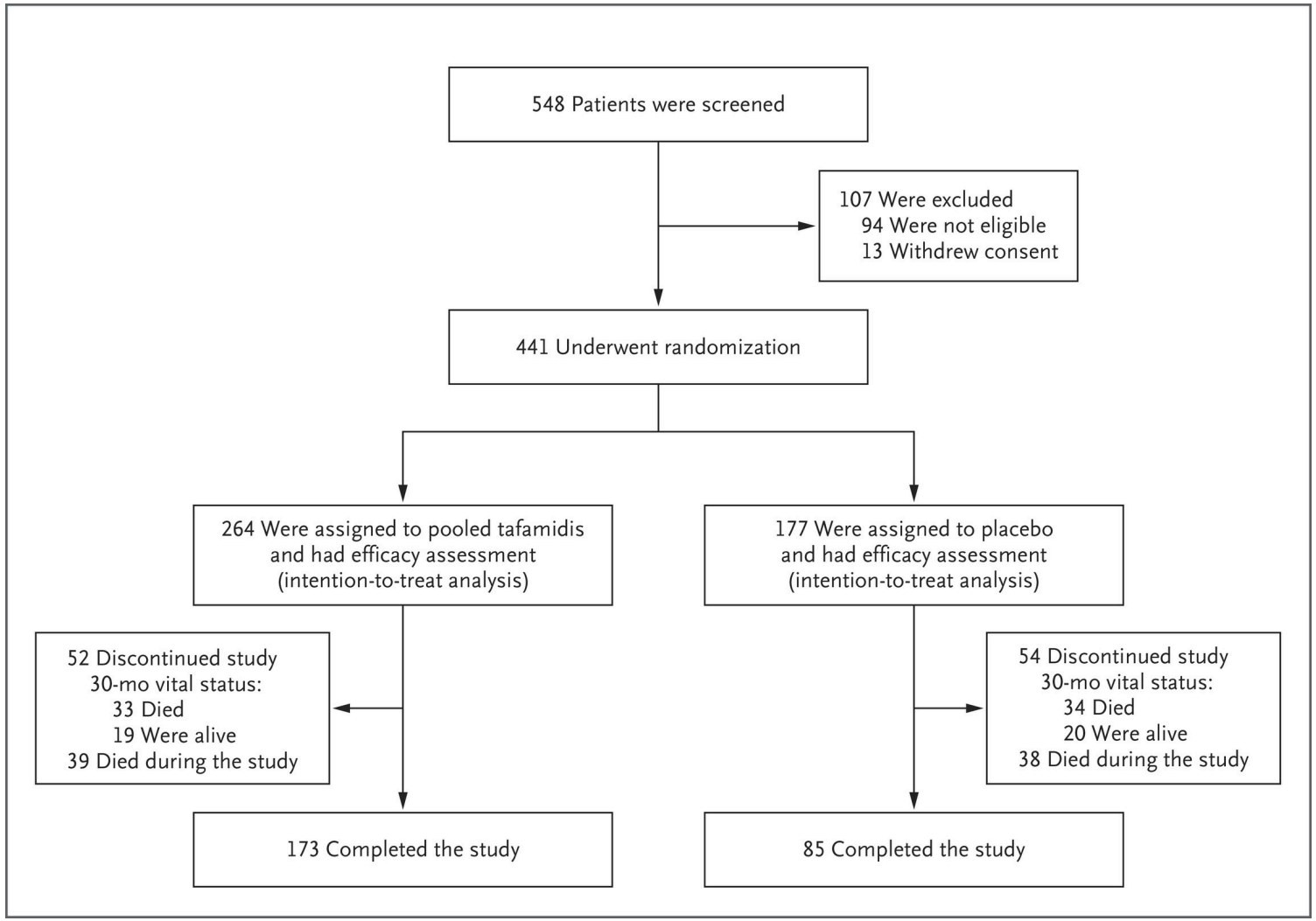
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 13, 2018 VOL. 379 NO. 11

Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

Mathew S. Maurer, M.D., Jeffrey H. Schwartz, Ph.D., Balarama Gundapaneni, M.S., Perry M. Elliott, M.D., Giampaolo Merlini, M.D., Ph.D., Marcia Waddington-Cruz, M.D., Arnt V. Kristen, M.D., Martha Grogan, M.D., Ronald Witteles, M.D., Thibaud Damy, M.D., Ph.D., Brian M. Drachman, M.D., Sanjiv J. Shah, M.D., Mazen Hanna, M.D., Daniel P. Judge, M.D., Alexandra I. Barsdorf, Ph.D., Peter Huber, R.Ph., Terrell A. Patterson, Ph.D., Steven Riley, Pharm.D., Ph.D., Jennifer Schumacher, Ph.D., Michelle Stewart, Ph.D., Marla B. Sultan, M.D., M.B.A., and Claudio Rapezzi, M.D., for the ATTR-ACT Study Investigators*

Randomization, Evaluation, and Outcomes.

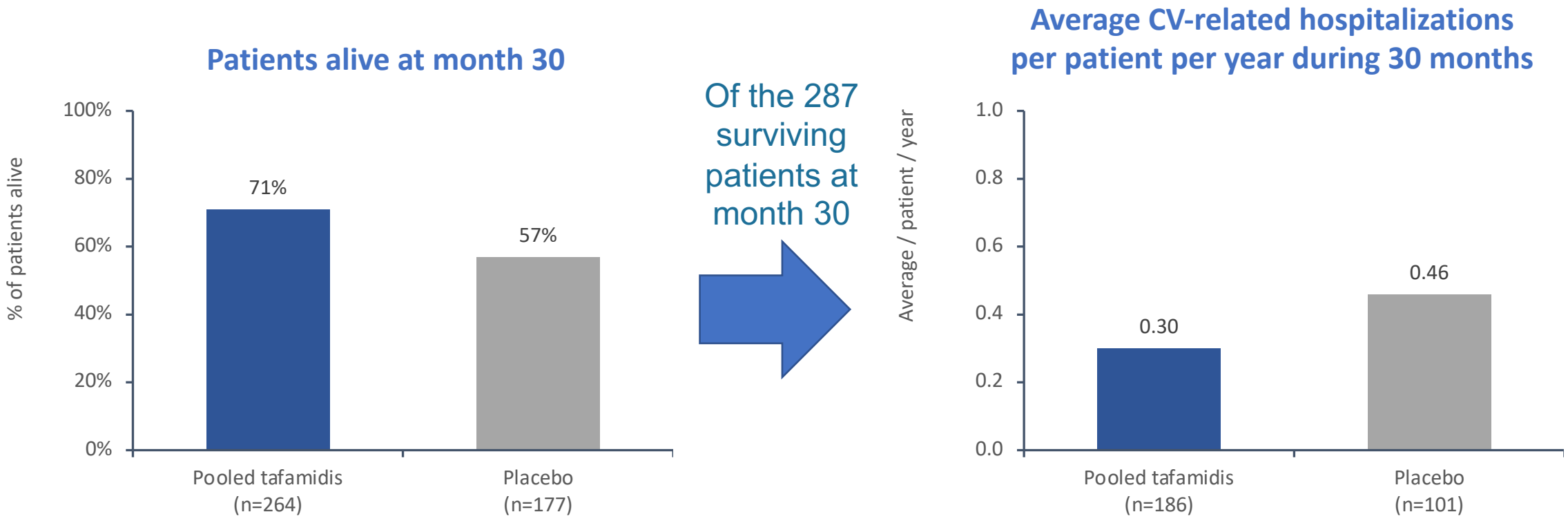


Maurer MS et al. N Engl J Med 2018;379:1007-1016

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Tafamidis (N=264)	Placebo (N=177)
Age — yr		
Mean	74.5±7.2	74.1±6.7
Median (range)	75 (46–88)	74 (51–89)
Sex — no. (%)		
Male	241 (91.3)	157 (88.7)
Female	23 (8.7)	20 (11.3)
Race — no. (%)		
White	211 (79.9)	146 (82.5)
Black	37 (14.0)	26 (14.7)
Asian	13 (4.9)	5 (2.8)
Other	3 (1.1)	0
TTR genotype — no. (%)		
ATTRm	63 (23.9)	43 (24.3)
ATTRwt	201 (76.1)	134 (75.7)
Blood pressure — mm Hg		
Supine		
Systolic	115.4±15.4	115.1±15.7
Diastolic	70.4±10.3	70.2±9.5
Standing		
Systolic	115.5±15.5	115.9±15.9
Diastolic	70.6±9.9	71.0±10.3
Heart rate, mean — beats per minute		
Supine	70.7±12.3	69.9±11.7
Standing	72.9±12.9	73.8±12.2
NYHA Class — no. (%)		
Class I	24 (9.1)	13 (7.3)
Class II	162 (61.4)	101 (57.1)
Class III	78 (29.5)	63 (35.6)
Modified BMI†	1058.8±173.8	1066.4±194.4
NT-proBNP level — pg/ml		
Median	2995.9	3161.0
Interquartile range	1751.5–4861.5	1864.4–4825.0

Significant Reduction of All-Cause Mortality and Frequency of CV-Related Hospitalizations with Tafamidis vs Placebo Over 30 Months (p=0.0006)



Adapted from Maurer MS, et al. *N Engl J Med* 2018; 379:1007–16.
Pfizer Canada ULC. PrVYNDAQEL™ product monograph.

Primary Analysis and Components.

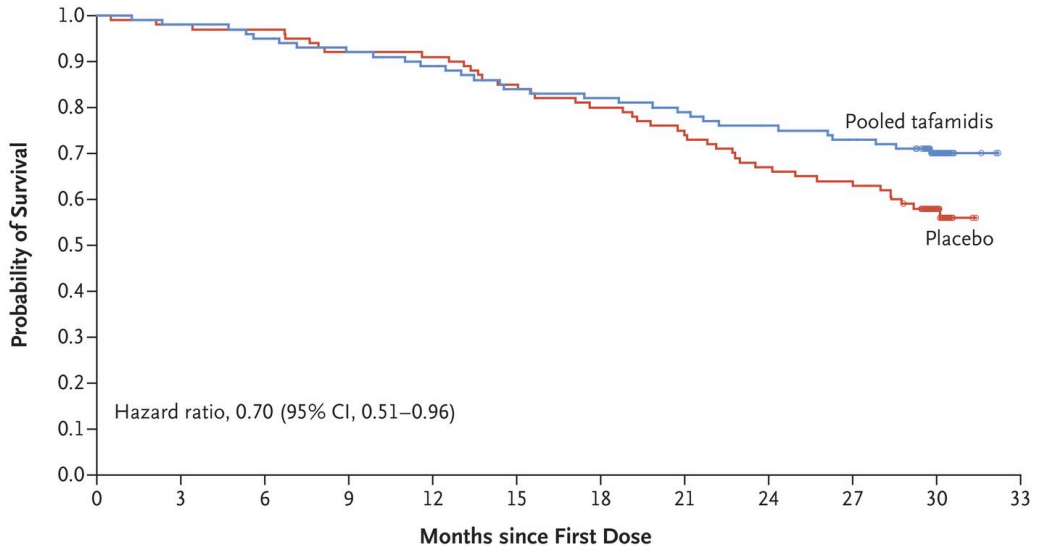
A Primary Analysis, with Finkelstein–Schoenfeld Method

	No. of Patients	P Value from Finkelstein–Schoenfeld Method	Win Ratio (95% CI)	Patients Alive at Mo 30	Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30
				no. (%)	*per patient per yr*
Pooled Tafamidis	264	<0.001	1.70 (1.26–2.29)	186 (70.5)	0.30
Placebo	177			101 (57.1)	0.46

C Frequency of Cardiovascular-Related Hospitalizations

	No. of Patients	No. of Patients with Cardiovascular- Related Hospitalizations	Cardiovascular- Related Hospitalizations	Pooled Tafamidis vs. Placebo Treatment Difference
		total no. (%)	*no. per yr*	*relative risk ratio (95% CI)*
Pooled Tafamidis	264	138 (52.3)	0.48	0.68 (0.56–0.81)
Placebo	177	107 (60.5)	0.70	

B Analysis of All-Cause Mortality

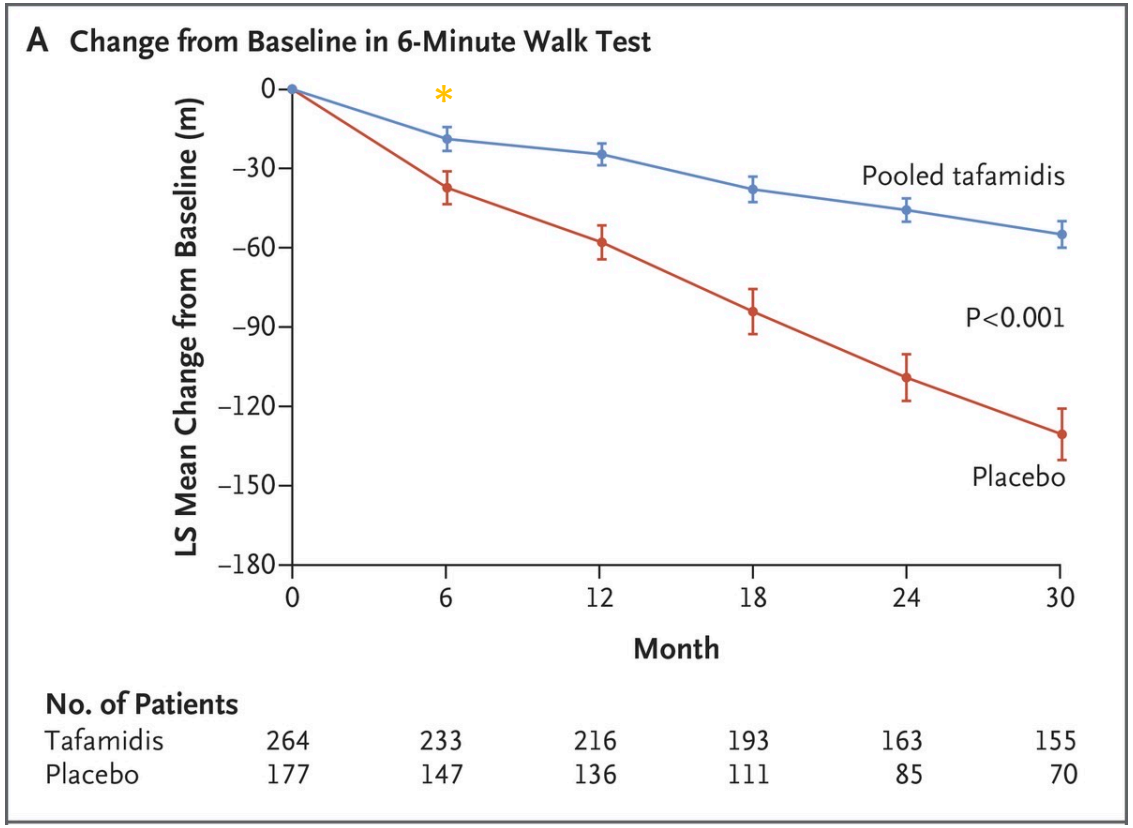


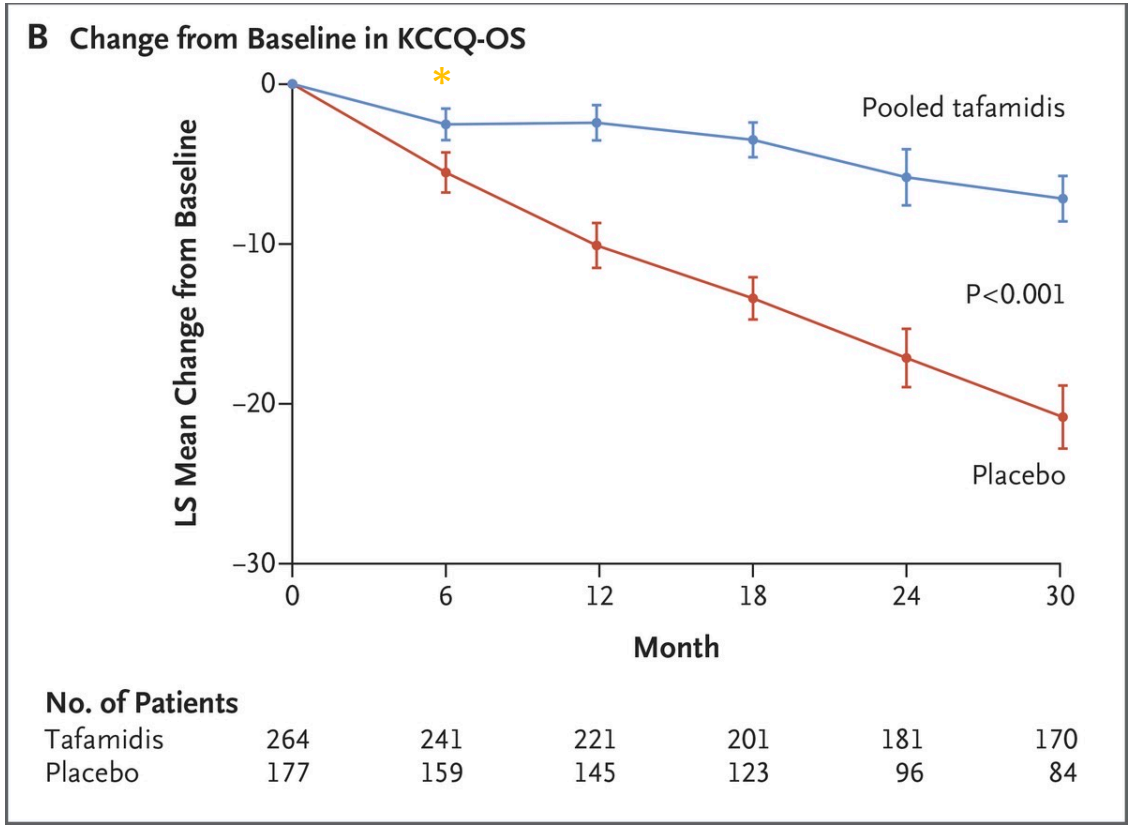
No. at Risk (cumulative no. of events)

Pooled tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)	0 (78)
Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)	0 (76)

Maurer MS et al. N Engl J Med 2018;379:1007-1016

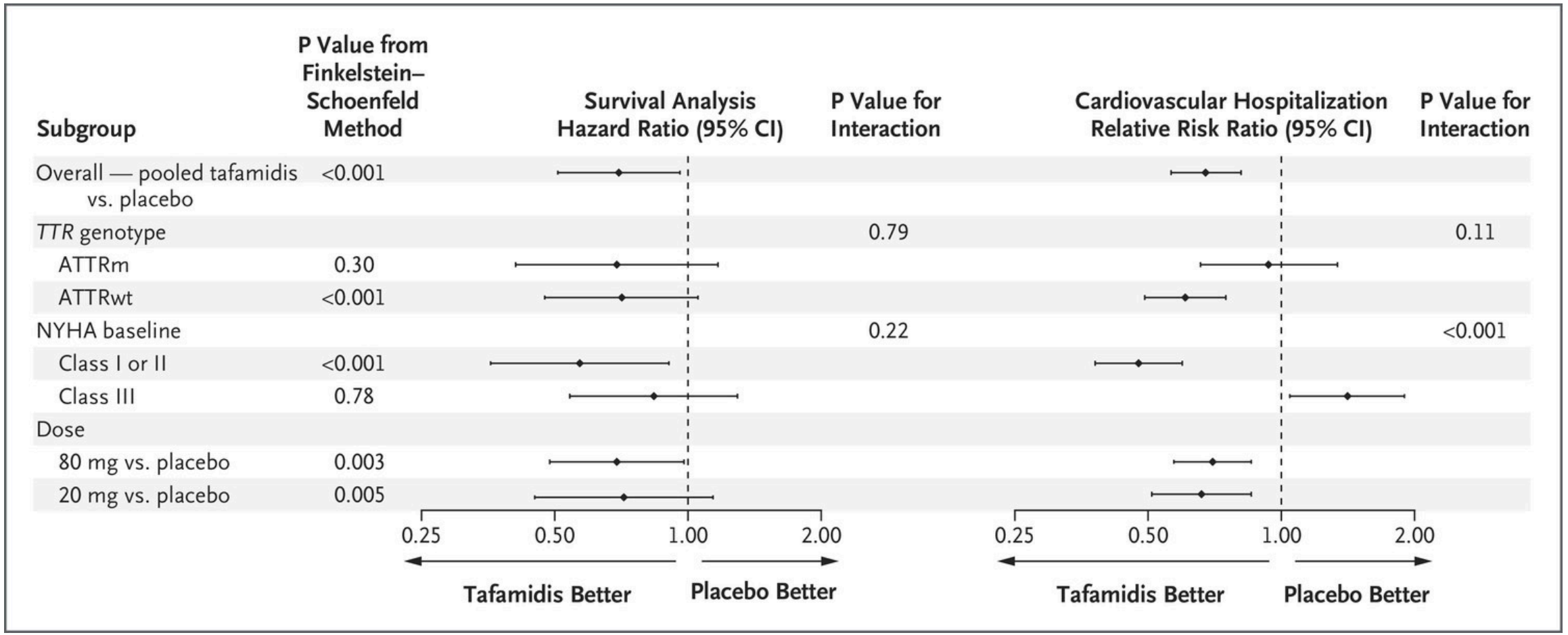
Key Secondary End Points





Maurer MS et al. N Engl J Med 2018;379:1007-1016

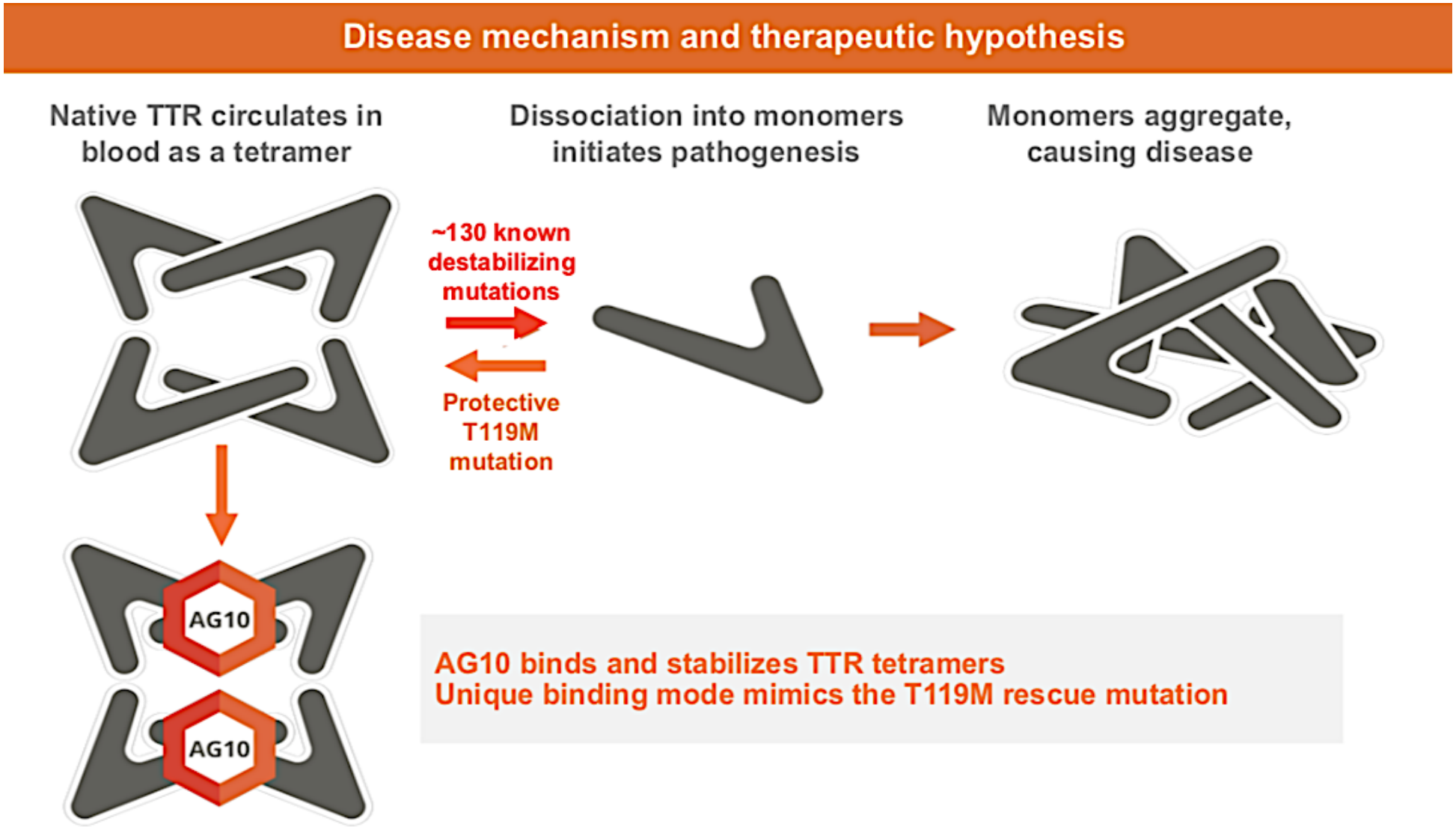
Tafamidis: Subgroup analysis



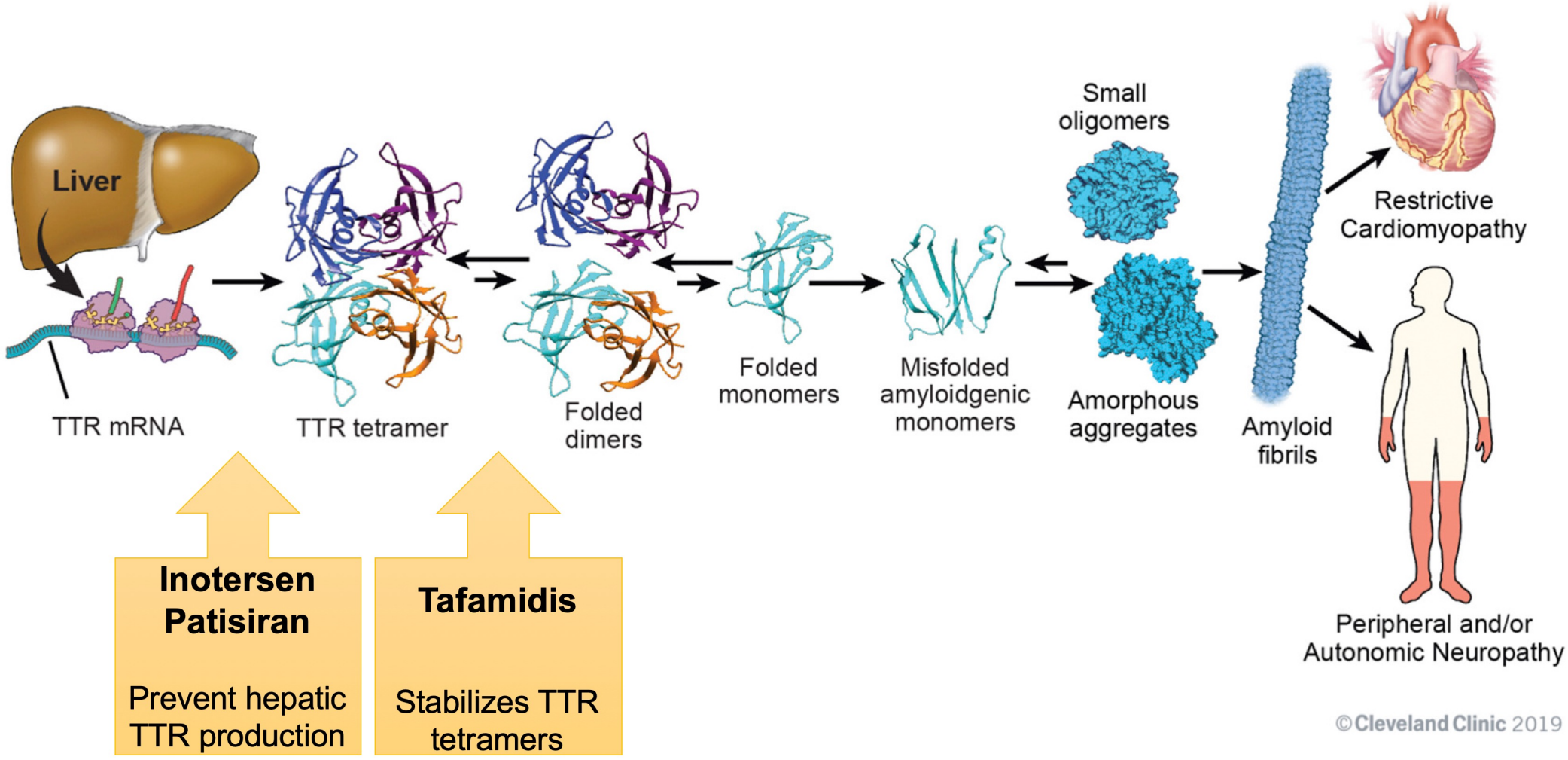
CI, confidence interval.

Adapted from Maurer MS et al. N Engl J Med 2018; Epub ahead of print doi: 10.1056/NEJM/Moa1805689.

Emerging Small Molecule Treatment for TTR Amyloidosis: Stabilizers

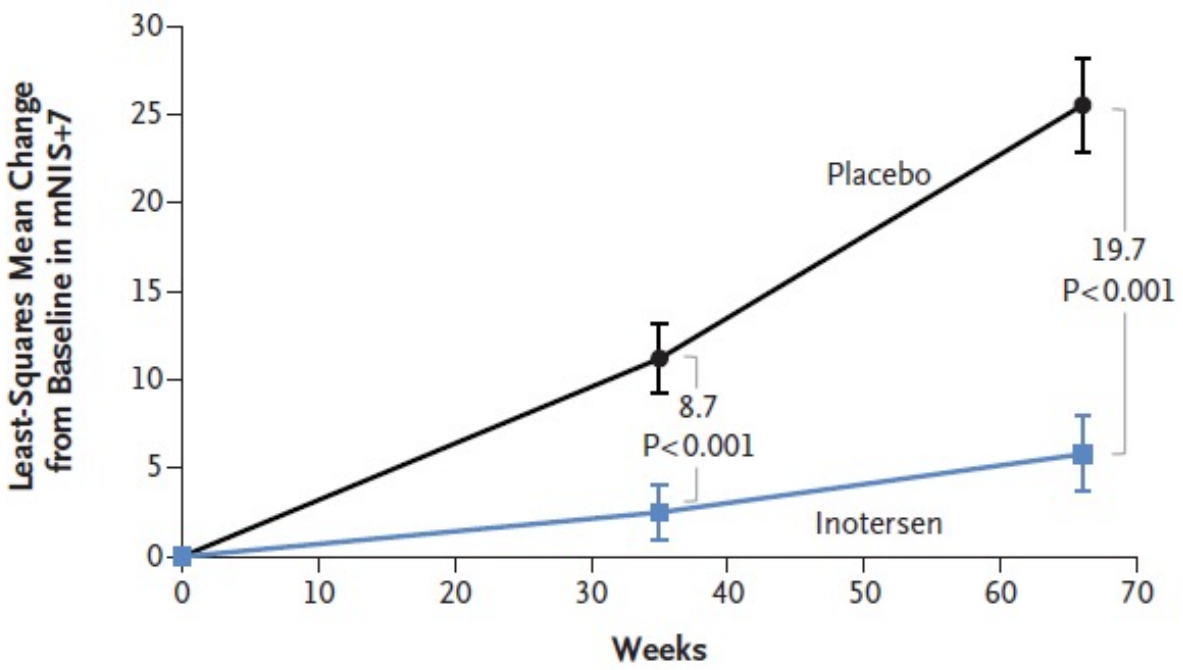


Therapeutic Targets of the Amyloidogenic TTR Cascade



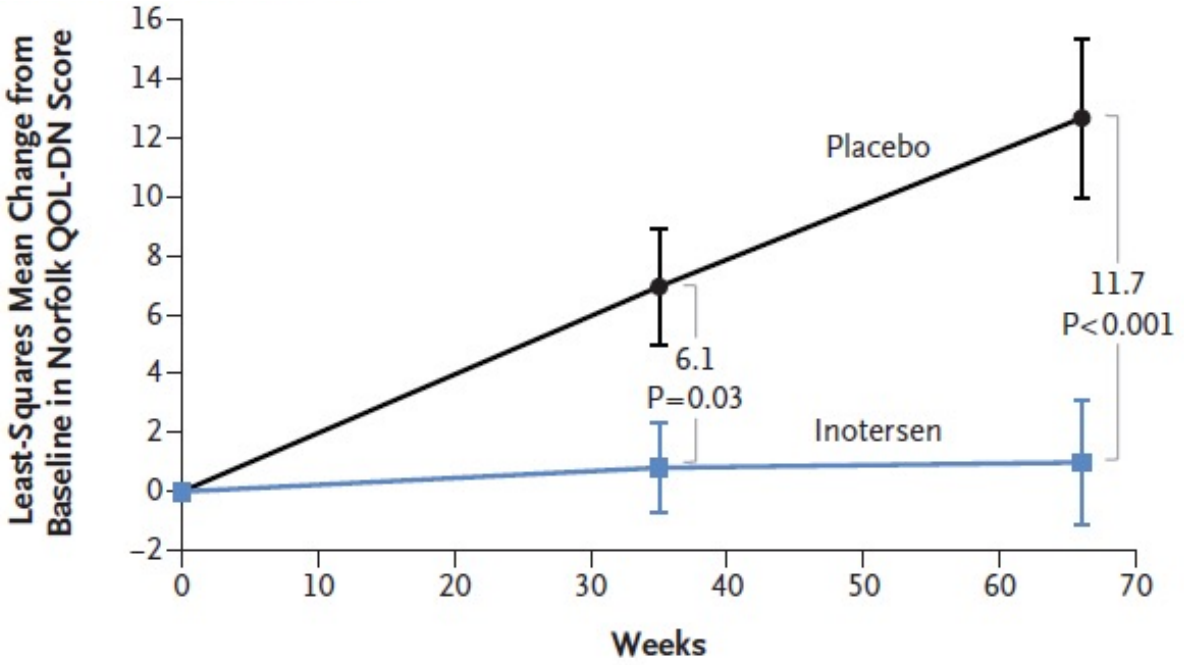
Inotersen: Change From Baseline in mNIS+7 and Norfolk QOL-DN Score Over 15 Months

mNIS+7



The higher the score, the poorer the function.

Norfolk QOL-DN

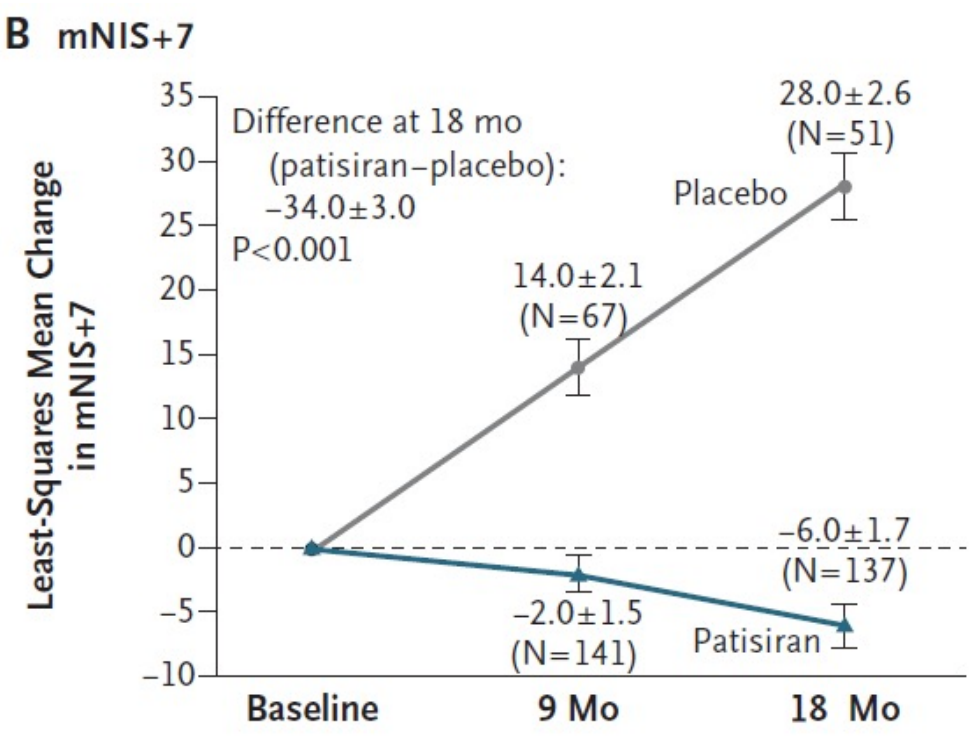


The higher the score, the poorer the QoL.
A decrease in score indicates an improvement in QoL.

mNIS+7, modified Neuropathy Impairment Score+7; QoL, quality of life; QOL-DN, Norfolk Quality of Life – Diabetic Neuropathy.
Adapted from Benson MD et al. N Engl J Med 2018;379(1):22-31.

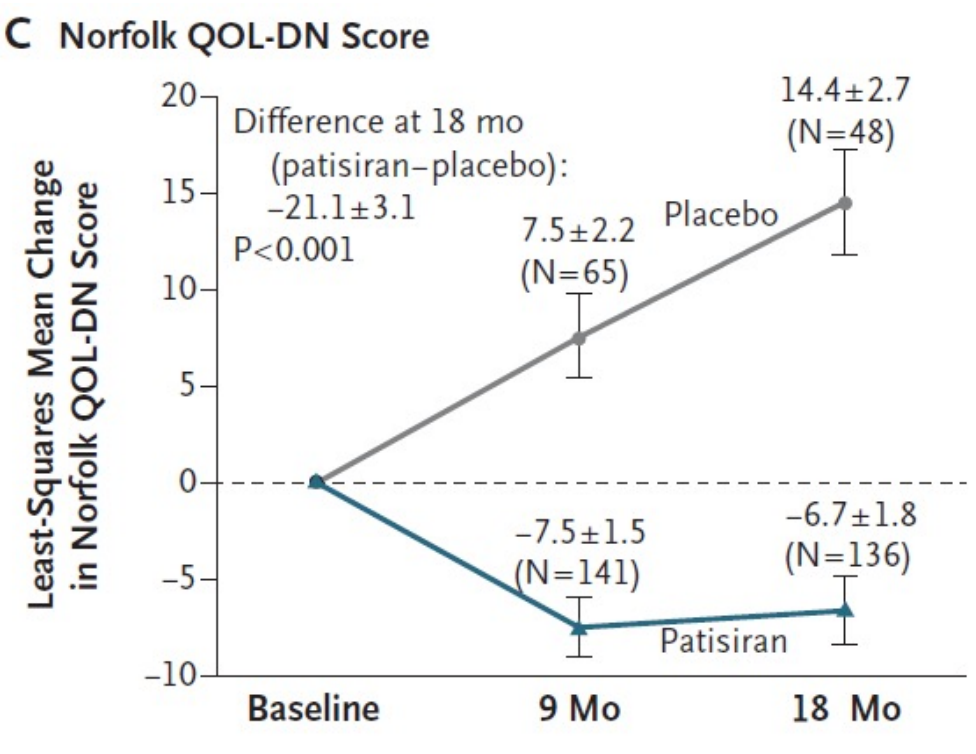
Patisiran: Change From Baseline in mNIS+7 and Norfolk QOL-DN Score Over 18 Months

mNIS+7



The higher the score, the poorer the function.
A decrease in score indicates an improvement in function.

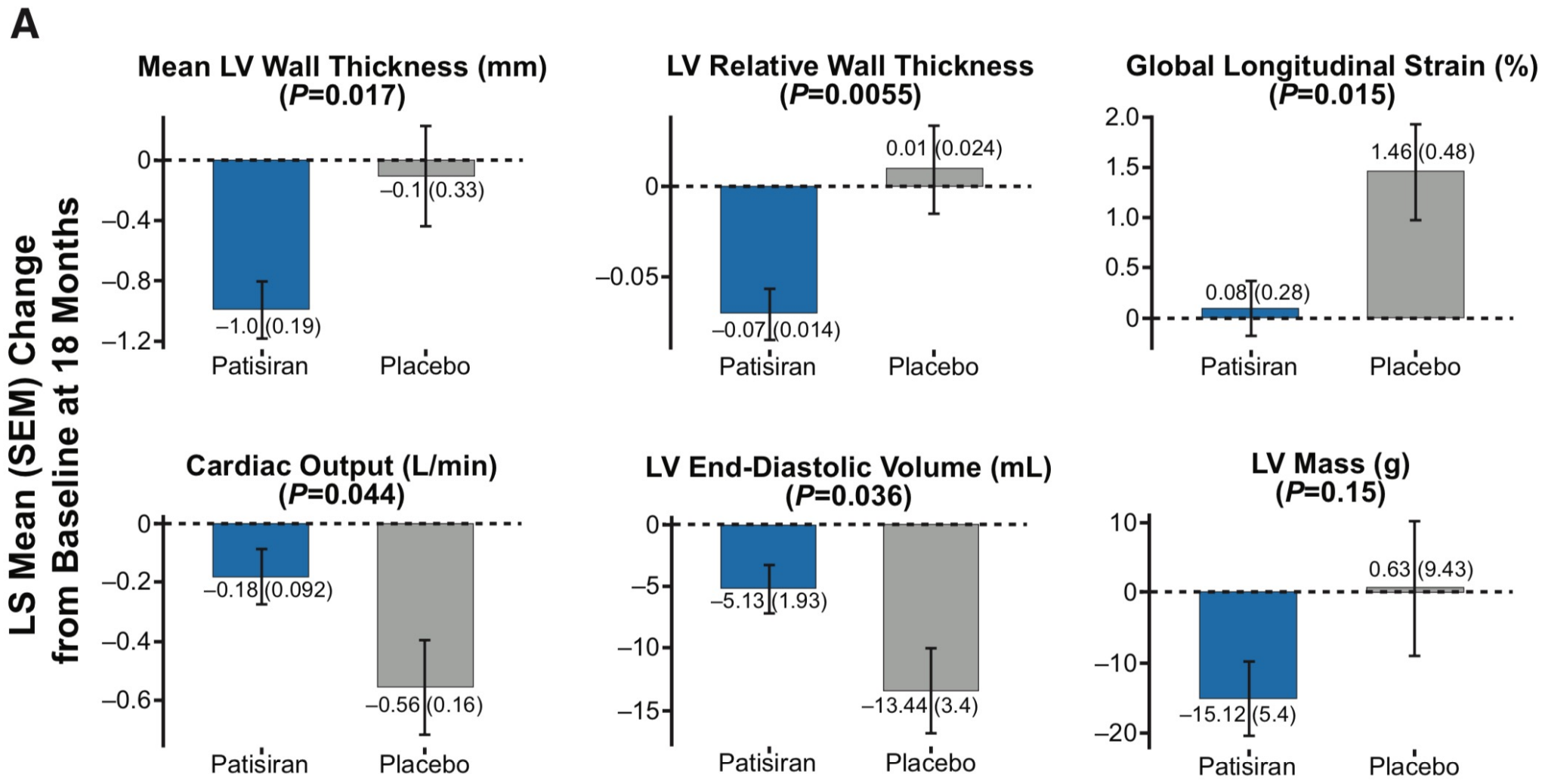
Norfolk QOL-DN



The higher the score, the poorer the QoL.
A decrease in score indicates an improvement in QoL.

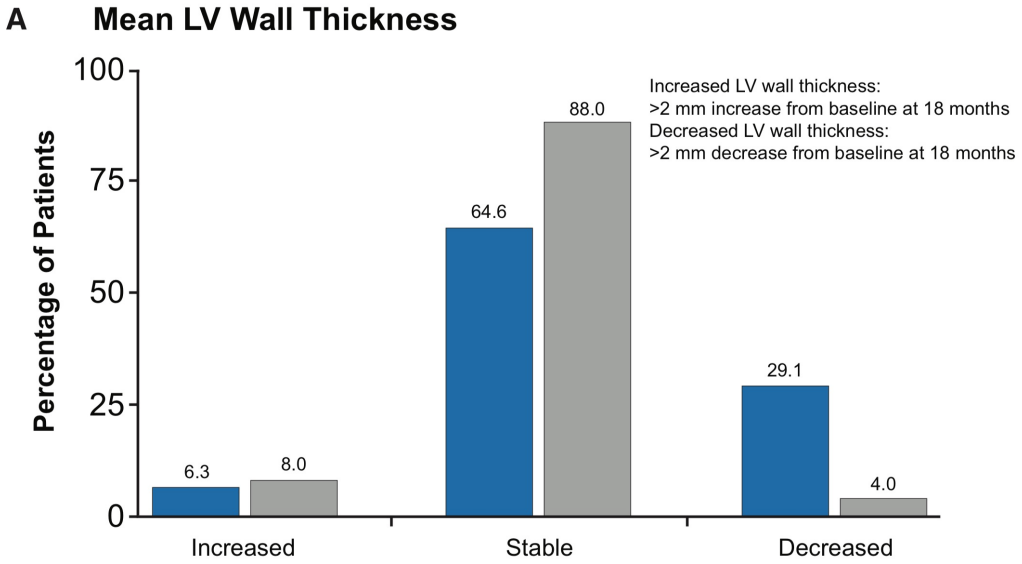
mo, months; mNIS+7, modified Neuropathy Impairment Score+7; QoL, quality o life; QOL-DN, Norfolk Quality of Life – Diabetic Neuropathy.
Adapted from Adam D et al. N Engl J Med 2018;379(1):11-21.

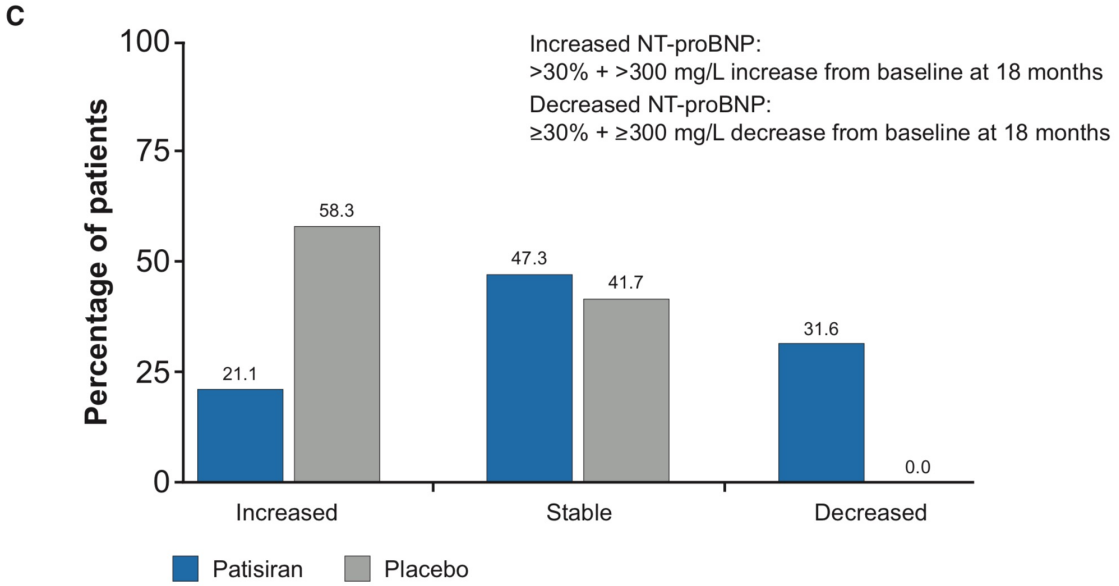
Patisiran: Cardiac Endpoints



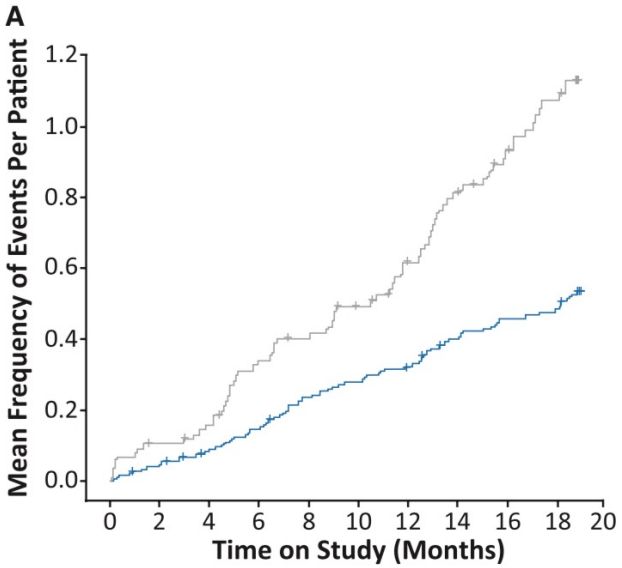
Circulation. 2019;139:431–443

Patisiran: Reversal of Disease & Clinical Outcomes

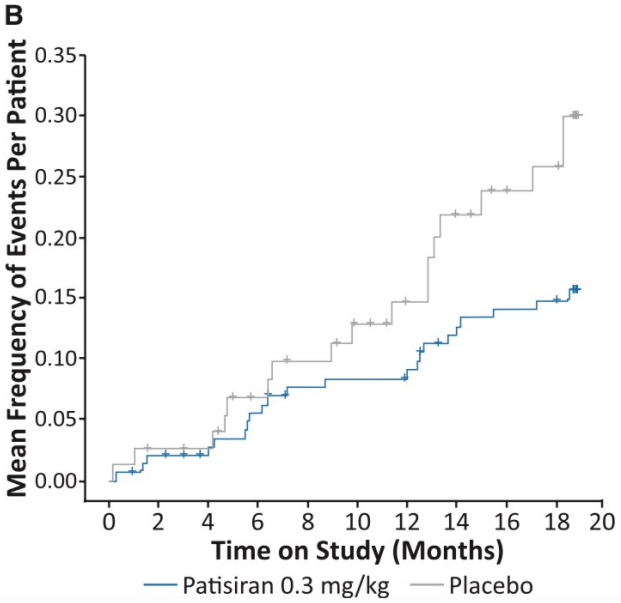




All-cause hospitalization and mortality



Cardiac hospitalization and all-cause mortality



Circulation. 2019;139:431–443

Disease modifying therapy in AL

AL Amyloid: Clinical Presentation

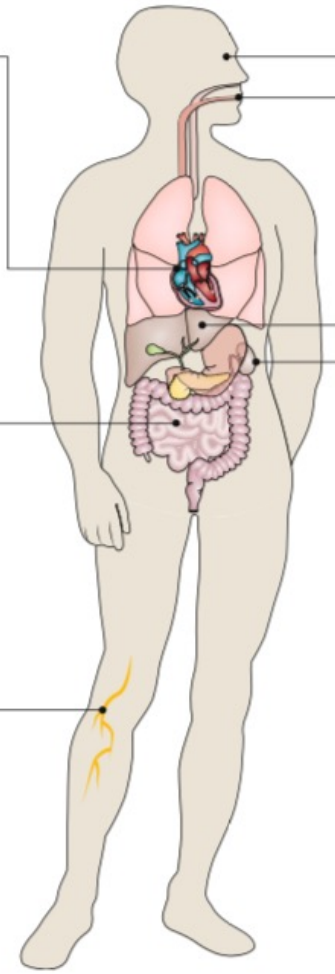
Death in >1/2 due to HF or arrhythmia

Heart
- Heart failure with preserved ejection fraction
- Thickened ventricular walls and low voltages on electrocardiography
- Dysponea at rest or exertion, fatigue
- Hypotension or syncope
- Peripheral oedema

Gastrointestinal tract
- Malabsorption and weight loss
- Bleeding (factor X)

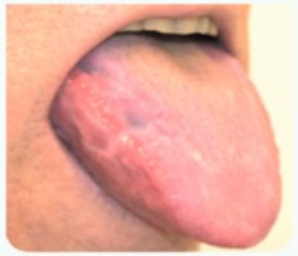
Nervous system
Peripheral
- Symmetric lower extremity sensorimotor polyneuropathy

Carpal tunnel syndrome (bilateral)
Autonomic
- Postural hypotension
- Erectile dysfunction (males)
- Gastrointestinal motility alterations



Periorbital purpura

Macroglossia

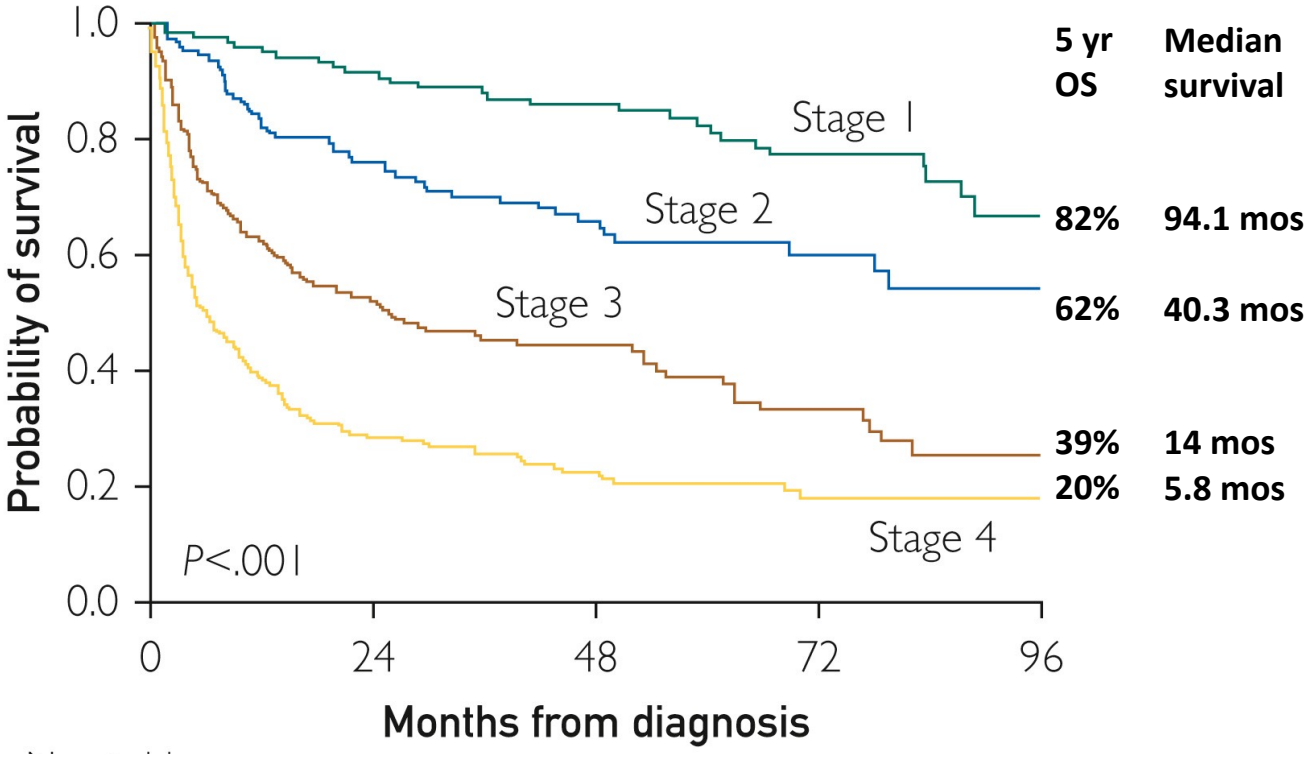


Liver
- Increased alkaline phosphatase
- Hepatomegaly

Kidney
- Nephrotic range proteinuria
- Renal failure
- Peripheral oedema

Nat Rev Dis Primers 4, 38 (2018).

Prognosis in AL: Revised Mayo Staging



dFLC ≥18 mg/dL

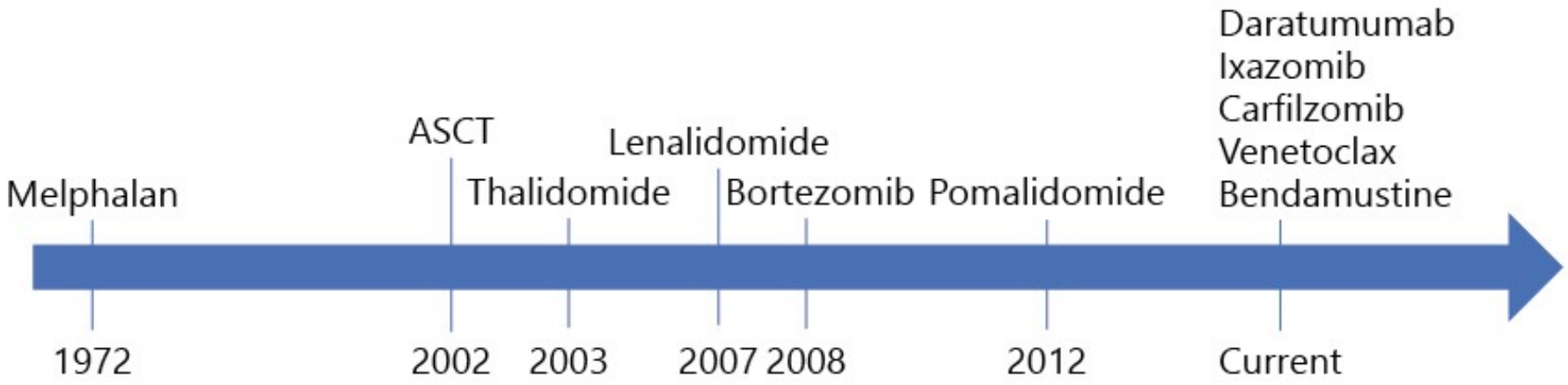
TnT ≥0.025

NT-proBNP ≥1800
or
BNP ≥400

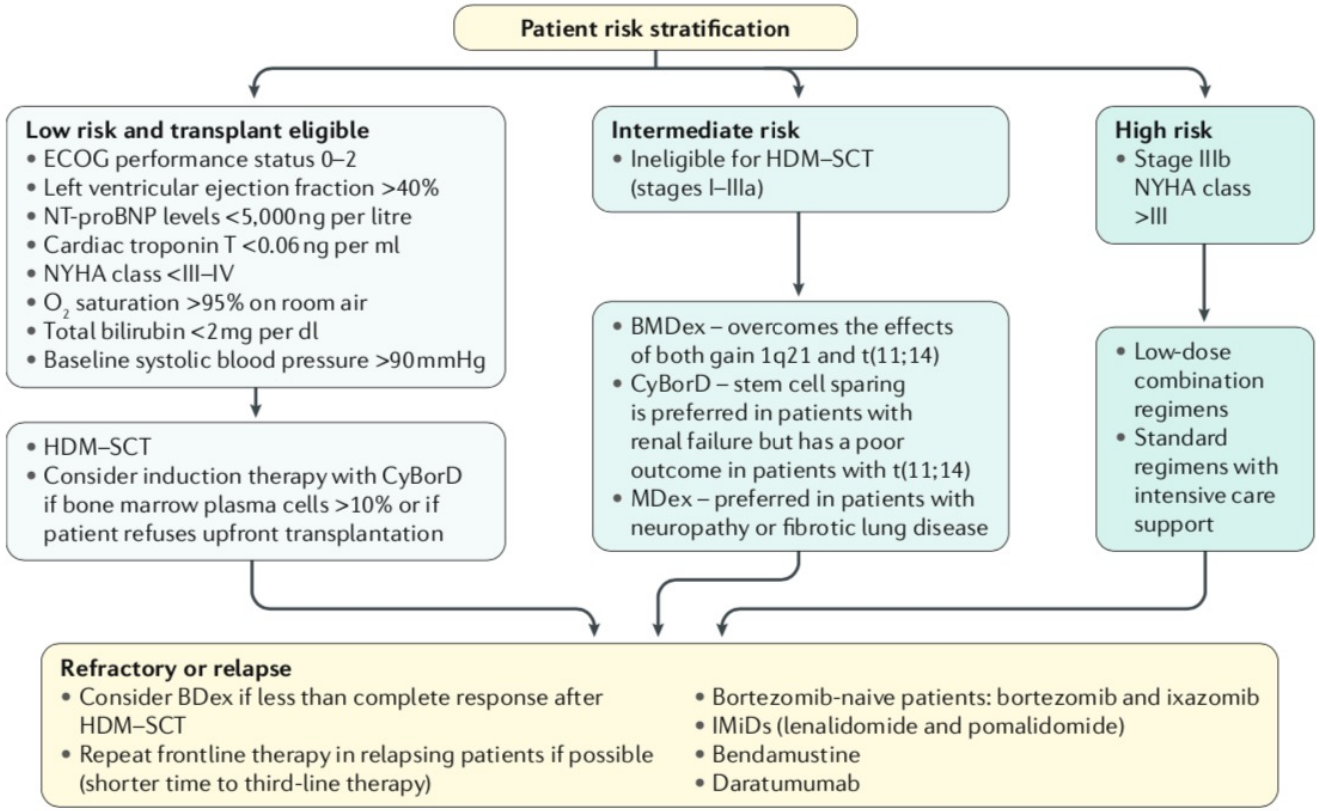
Stage 1: 0/3
Stage 2: 1/3
Stage 3: 2/3
Stage 4: 3/3

Mayo Clin Proc. 2019;94(3):472-483

Evolution of Therapy for AL



AL: Light chain-suppressive therapy



Nat Rev Dis Primers 4, 38 (2018).

Conclusions

- Cardiac amyloidosis is an underdiagnosed cause of heart disease
- Multiple diagnostic modalities can help to raise suspicion or confirm the diagnosis
- Novel therapies have shown considerable benefits and promise for the care of cardiac amyloidosis
- Additional therapies and advances in the diagnosis will continue to improve the care of this challenging and complex population